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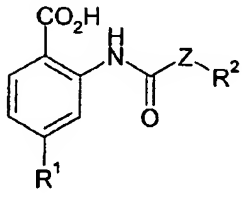
(54) Title: 2-SUBSTITUTED BENZOIC ACID DERIVATIVES AS HM74A RECEPTOR AGONISTS



(I)

(57) Abstract: Therapeutically active anthranilic acid derivatives of Formula (I) wherein R1, R2 and Z are as defined in the specification, processes for the preparation of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases in which under-activation of the HM74A receptor contributes to the disease or in which activation of the receptor will be beneficial, are disclosed.

WO 2005/016870 A1

2-SUBSTITUTED BENZOIC ACID DERIVATIVES AS HM74A RECEPTOR AGONISTS

The present invention relates to therapeutically active compounds which are anthranilic acid derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases in which under-activation of the HM74A receptor contributes to the disease or in which activation of the receptor will be beneficial.

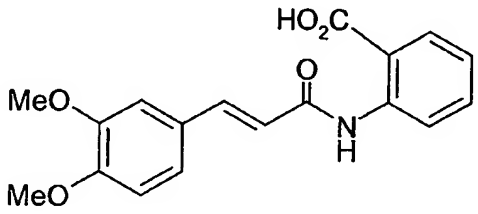
Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL), which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem. 2003 **278** (11) 9869-9874). The DNA sequence of human HM74A may be found in Genbank; accession number AY148884. Two other papers support this discovery, (Tunaru et. al. Nature Medicine 2003 (3) 352-255 and Soga et. al. Biochem Biophys Res Commun. 2003 **303** (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 is in fact HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

Certain anthranilic acid derivatives have been synthesised and disclosed in the prior art; some of these compounds have been shown to have utility in therapy, as outlined below.

H. Brauniger et al. (1977) Pharmazie 32, 150-154 relates to synthesis of benzoxazine derivatives. It specifically discloses certain para-substituted phenyl-propanoyl-aminobenzoic acid derivatives as intermediates in the synthesis, but no therapeutic use is mentioned.

WO 01/25190 A1 relates to diaryl amide derivatives and the use thereof as medicines. It specifically discloses certain anthranilic acid derivatives, in particular compound X:



X.

is disclosed as a synthetic intermediate.

WO 97/30019 A1 relates to aniline derivatives as antihyperglycemic or anti-diabetic compounds. It specifically discloses 2-(2-(((4-(phenyl)phenyl)amino)acetyl)amino) benzoic acid and 2-(2-(((4-phenyl)phenoxy)acetyl)amino)benzoic acid.

We now present a group of anthranilic acid derivatives which are selective agonists of the nicotinic acid receptor HM74A and are thus of benefit in the treatment, prophylaxis and suppression of diseases where under-activation of this receptor either contributes to the disease or where activation of the receptor will be beneficial.

Summary of the Invention

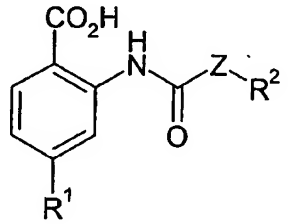
The present invention provides therapeutically active anthranilic acid derivatives and the use of these derivatives in therapy, particularly in the treatment of diseases in which under-activation of the HM74A receptor contributes to the disease or in which activation of the receptor will be beneficial, in particular diseases of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I

diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

Intermediates, formulations, methods and processes described herein form further aspects of the invention.

Detailed Description of the Invention

The present invention provides a compound of Formula (I)



(I)

and salts, solvates and physiologically functional derivatives thereof, wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

Z represents $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_nO-$; $-C(R^4R^5)O-$ or -Y-W-X- ;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$; $-(CH_2)_pS-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 and 2;

q represents an integer selected from 1, 2, 3 and 4;

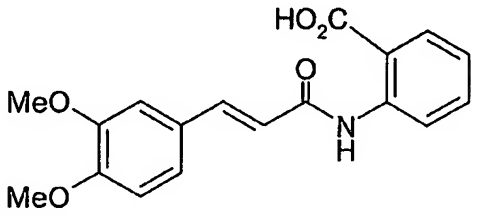
R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl;

provided

(i) that when R^1 is hydrogen, Z is $-(CH_2)_n-$, and n is 2, then R^2 is other than para-chlorophenyl or para-methylphenyl;

(ii) that a compound of Formula (I) is other than 2-(2-(((4-(phenyl)phenyl) amino)acetyl)amino)benzoic acid, 2-(2-(((4-phenyl)phenoxy)acetyl)amino) benzoic acid, 2-[[(4-cyclohexylphenoxy)acetyl]amino]benzoic acid, 2-[[3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxopropyl]amino]benzoic acid or compound X



X.

In compounds of the present invention, the R^2 ring system may be joined to the Z linker unit via either a ring carbon atom or via a ring heteroatom, where present.

In certain embodiments of the present invention, R^1 groups are hydrogen or C_1-C_3alkyl, for example hydrogen or methyl.

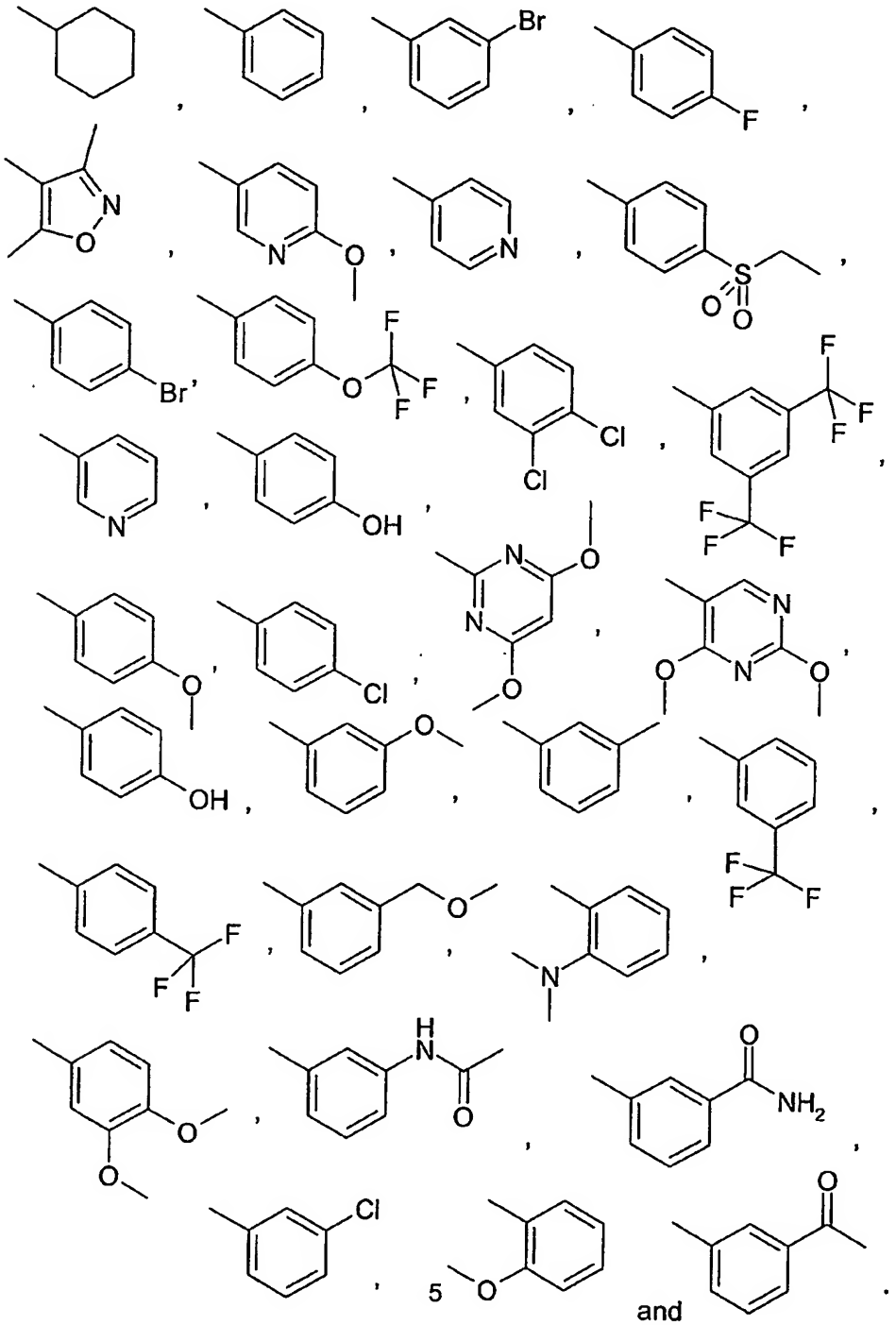
In certain embodiments in which R^2 is heteroaryl, R^2 is selected from pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, oxazolyl and isoxazolyl. In certain embodiments in which R^2 is heterocyclic, R^2 is selected from pyrrolidinyl, imidazolidinyl, piperidinyl and morpholinyl.

In further embodiments, R^2 is selected from cyclohexyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl and isoxazolyl. As defined below, the 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic R^2 groups may be substituted and thus include substituted cyclohexyl, substituted phenyl, substituted pyridine, substituted pyrimidine, substituted pyridazine or substituted isoxazole, in which the substituents are as defined further below.

Thus, where R^2 is substituted phenyl, the substituents will be those defined for "aryl" substituents below. In some embodiments the substituted phenyl bears one or two substituents selected from halogen C_{1-3}alkyl (for example methylphenyl), C_{1-3}haloalkyl (for example trifluoroalkyl including trifluoromethylphenyl), C_{1-3}alkoxy (for example methoxyphenyl) and C_{1-3}haloakloxy (for example trifluoroalkoxy including trifluoromethoxyphenyl).

In certain embodiments in which R^2 represents singly substituted phenyl, the substituent is at the meta or para position, for example para. In certain embodiments in which R^2 represents doubly substituted phenyl, the substituents are at the para and meta, or at both meta positions.

In certain embodiments, R^2 is selected from the group consisting of:



and

In certain embodiments of the present invention, Z represents –Y-W-X–, $-(CH_2)_q-$, $-(CH_2)_nO-$ or $-(CH_2)_pNHC(O)-$.

In certain embodiments Y represents –O– , $-CH_2-$ or $-CH_2O-$. In particular embodiments, X is absent or represents $-(CH_2)_pSO_2NR^3-$, $-(CH_2)_pNHC(O)-$ or $-(CH_2)_pNHC(O)NH-$. In certain embodiments in which Y represents $-CH_2-$, X represents $-(CH_2)_pSO_2NR^3-$. In certain embodiments in which Y represents –O– or $-CH_2O-$, X is absent.

Particular W groups are 5 or 6 member aryl or heteroaryl rings. In certain embodiments in which W is aryl, for example C6 aryl (e.g. phenyl), W is linked through the 1 and 4 or the 1 and 3 positions. In certain embodiments in which W is heteroaryl, for example a 5 member heteroaryl ring (e.g. 1, 2, 4 oxadiazolyl), W may be linked through the 3 and 5 positions. In other embodiments in which W is heteroaryl, for example a 6 member heteroaryl ring (e.g. pyridinyl), W may be linked through the 2 and 5 positions. When X is $-(CH_2)_pSO_2NR^3-$, p is 0 and W is unsubstituted phenyl, W may for example be linked through the 1 and 4 (para) positions.

In certain embodiments, n represents 2.

In certain embodiments, p represents an integer selected from 0 or 1.

In certain embodiments W and R^2 each represent unsubstituted phenyl, whilst in other embodiments W represents unsubstituted phenyl and R^2 represents substituted phenyl.

It is to be understood that the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described hereinabove.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to an optionally substituted straight or branched hydrocarbon chain containing the specified number of carbon atoms. For example, C_1-C_3alkyl means a straight or branched hydrocarbon chain containing at least 1 and at most 3 carbon atoms. Examples of alkyl as used herein include, but are not limited to; methyl (Me), ethyl (Et), n-propyl, i-propyl and the like. Unless otherwise stated, optional substituents include hydroxy, halogen, =S and =O.

As used herein, the term "alkoxy" (when used as a group or as part of a group) refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of alkoxy as used herein include, but are not limited to; methoxy, ethoxy, n-propoxy, i-propoxy and the like.

As used herein, the term "alicyclic" (when used as a group or as part of a group) refers to a cyclic hydrocarbon ring containing the specified number of carbon atoms. Examples of alicyclic as used herein include, but are not limited to cyclohexyl, cyclopropyl and the like. Said alicyclic groups may be optionally substituted with one or more, for example 1 to 3, groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "aryl" (when used as a group or as part of a group) refers to an aromatic hydrocarbon ring of the specified number of carbons. Examples of aryl as used herein include, but are not limited to, phenyl and benzyl. Said aryl groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "heteroaryl" (when used as a group or as part of a group) refers to an aryl group, as defined above, which contains one or more nitrogen or oxygen heteroatoms. Examples of heteroaryl as used herein include, but are not limited to, pyridine, pyrimidine, pyridazine, imidazole, isoxazole, oxadiazoles and the like. Said heteroaryl groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "heterocyclic" (when used as a group or as part of a group) refers to an alicyclic group, as defined above, which contains one or more nitrogen or oxygen heteroatoms. Said heterocyclic groups may be optionally substituted with one or more, for example 1 to 3 groups selected from hydroxy, halogen, =S, =O, C_1-C_3alkyl (which may be further substituted with one or more hydroxy, =O or halo groups), optionally halogenated C_1-C_3alkoxy, C_1-C_3alkoxyC_1-C_3alkyl, NR^3_2, -$NHC(O)C_1$-C_3alkyl, -$C(O)NR^3_2$, and -$S(O)_2C_1$-C_3alkyl, wherein R^3 is as defined above.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example an ester or an amide thereof, and includes any pharmaceutically acceptable salt, ester, or salt of such ester of a compound of Formula (I) which, upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) a compound of Formula (I) or an active metabolite or residue thereof. It will be appreciated by those skilled in the art that the compounds of Formula (I) may be modified to provide physiologically functional derivatives thereof at any of the functional groups in the compounds, and that the compounds of Formula (I) may be so modified at more than one position.

As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient or excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

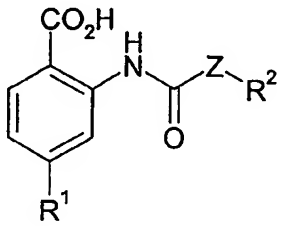
As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I), a salt thereof or a physiologically functional derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water, in which case the solvate may be referred to as a hydrate of the solute in question.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of Formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable

salts include acid addition salts formed from the addition of inorganic acids or organic acids, preferably inorganic acids. Examples of suitable acid addition salts include hydrochlorides, hydrobromides, sulphates and acetates. Further representative examples of pharmaceutically acceptable salts include those formed from maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, cyclohexylsulfamic, phosphoric and nitric acids. Suitable pharmaceutically acceptable salts also include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. An example of a suitable alkali metal salt is a sodium salt.

In a further aspect, the present invention provides the use of a compound of Formula (Ia)



(Ia)

and salts, solvates and physiologically functional derivatives thereof in the manufacture of a medicament for the treatment of disorders of lipid metabolism, including dislipidaemia or hyperlipoproteinaemia, or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 and 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5, which may be the same or different, independently represent C_1-C_3alkyl.

In compounds of Formula (Ia), as set out for compounds of Formula (I) above, the R^2 ring system may be joined to the Z linker unit via either a ring carbon atom or via a ring heteroatom; where present.

In certain embodiments, R^1 groups are hydrogen or C_1-C_3alkyl, for example hydrogen or methyl.

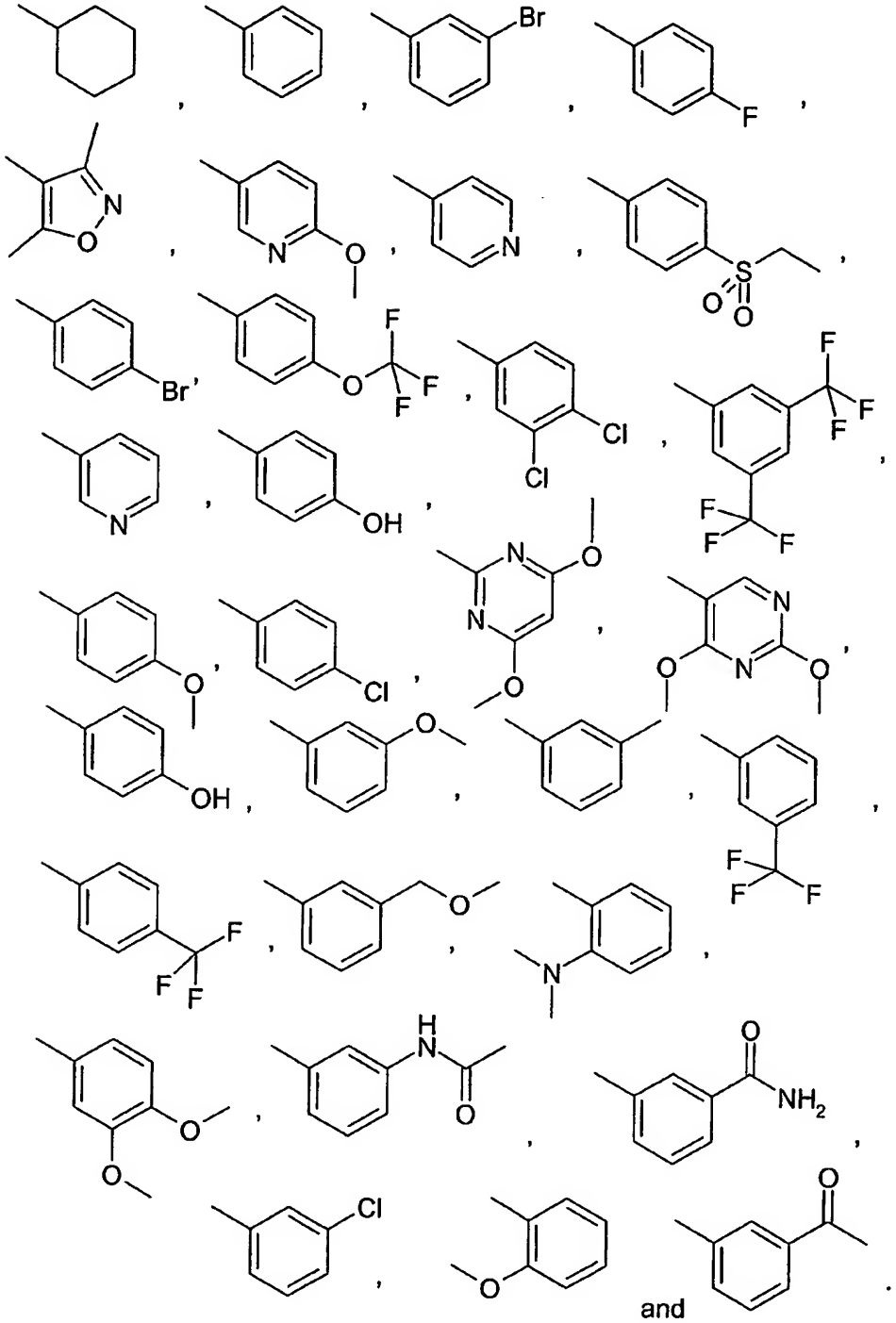
In certain embodiments in which R^2 is heteroaryl, R^2 is selected from pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrazolyl, imidazolyl, oxazolyl and isoxazolyl. In certain embodiments in which R^2 is heterocyclic, R^2 is selected from pyrrolidinyl, imidazolidinyl, piperidinyl and morpholinyl.

In further embodiments, R^2 is selected from cyclohexyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl and isoxazolyl. As defined below, the 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic R^2 groups may be substituted and thus include substituted cyclohexyl, substituted phenyl, substituted pyridine, substituted pyrimidine, substituted pyridazine or substituted isoxazole, in which the substituents are as defined above.

Thus, where R^2 is substituted phenyl, the substituents will be those defined for "aryl" substituents above. In some embodiments the substituted phenyl bears one or two substituents selected from halogen C_{1-3}alkyl (for example methylphenyl), C_{1-3}haloalkyl (for example trifluoroalkyl including trifluoromethylphenyl), C_{1-3}alkoxy (for example methoxyphenyl) and C_{1-3}haloakloxy (for example trifluoroalkoxy including trifluoromethoxyphenyl).

In certain embodiments in which R^2 represents singly substituted phenyl, the substituent is at the meta or para position, for example para. In certain embodiments in which R^2 represents doubly substituted phenyl, the substituents are at the para and meta, or at both meta positions.

In certain embodiments, R^2 is selected from the group consisting of:



and

In certain embodiments, Z represents –Y-W-X–, $-(CH_2)_q-$, $-(CH_2)_nO-$ or $-(CH_2)_pNHC(O)-$.

In certain embodiments Y represents –O– , $-CH_2-$ or $-CH_2O-$. In particular embodiments, X is absent or represents $-(CH_2)_pSO_2NR^3-$, $-(CH_2)_pNHC(O)-$ or $-(CH_2)_pNHC(O)NH-$. In certain embodiments in which Y represents $-CH_2-$, X represents $-(CH_2)_pSO_2NR^3-$. In certain embodiments in which Y represents –O– or $-CH_2O-$, X is absent.

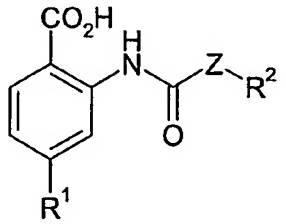
Particular W groups are 5 or 6 member aryl or heteroaryl rings. In certain embodiments in which W is aryl, for example C6 aryl (e.g. phenyl), W is linked through the 1 and 4 or the 1 and 3 positions. In certain embodiments in which W is heteroaryl, for example a 5 member heteroaryl ring (e.g. 1, 2, 4 oxadiazolyl), W may be linked through the 3 and 5 positions. In other embodiments in which W is heteroaryl, for example a 6 member heteroaryl ring (e.g. pyridinyl), W may be linked through the 2 and 5 positions. When X is $-(CH_2)_pSO_2NR^3-$, p is 0 and W is unsubstituted phenyl, W may for example be linked through the 1 and 4 (para) positions.

In certain embodiments, n represents 2.

In certain embodiments, p represents an integer selected from 0 or 1.

In certain embodiments W and R^2 each represent unsubstituted phenyl, whilst in other embodiments W represents unsubstituted phenyl and R^2 represents substituted phenyl.

This aspect of the invention also provides the use of a compound of Formula (I)



(I)

and salts, solvates and physiologically functional derivatives thereof as define above in the manufacture of a medicament for the treatment of disorders of lipid metabolism, including dislipidaemia or hyperlipoproteinaemia, or of inflammatory diseases or conditions. It is to be understood that this aspect of the present invention includes, with respect to the use of compounds of Formula (I) or of Formula (Ia) in the manufacture of a medicament, any combination of particular embodiments and covers

all combinations of particular substituents of compounds of Formula (I) or of Formula (Ia) described hereinabove.

Compounds of the present invention are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The use of a compound of Formula (Ia) in the treatment of one or more of these diseases is a further aspect of the present invention.

Furthermore, it is also believed that the HM74 and HM74A receptors are involved in inflammation. Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation and can last up to a lifetime. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic inflammation and allow for the physiological process of healing and tissue repair to progress.

Thus, a further aspect of the present invention resides in the use of a compound of Formula (Ia) or a salt, solvate or physiologically functional derivative thereof as defined above in the treatment of inflammatory diseases or conditions of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof), of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and

following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In particular, the compounds of Formula (Ia) are useful in the treatment and prevention of inflammation, and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

Thus, there is also provided the use of a compound of Formula (Ia) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. The compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity.

Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. The compounds of the present invention preferably exhibit reduced side effects compared to nicotinic acid.

HM74A has been identified as a high affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention are selective for HM74A by which is meant that they show greater affinity for HM74A than for HM74.

The potential for compounds of Formula (I) to activate HM74A may be demonstrated, for example, using the following *in vitro* and *in vivo* assays:

In-vitro testing

For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10% foetal calf serum and 2mM glutamine. Cells were seeded in 90mm culture dishes and grown to 60-80% confluence (18-24h) prior to transfection. Human HM74A (GenBank™ accession number AY148884) was subcloned in to a mammalian expression vector (pcDNA3; Invitrogen) and transfected using Lipofectamine reagent. For transfection, 9μg of DNA was mixed with 30μl Lipofectamine in 0.6ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 30min prior to the addition of 1.6ml of Opti-MEM. Cells were exposed to the Lipofectamine/DNA mixture for 5h and 6ml of

20% (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50ngml^{-1} for 16h. All transient transfection studies involved co-transfection of receptor together with the $G_{i/o}$ G protein, $G_{o1}\alpha$.

For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30% confluence. These cells were maintained in DMEM F-12 HAM media containing 10% foetal calf serum and 2mM glutamine. 48h post-transfection the media was supplemented with 400µg/ml Geneticin (G418, Gibco) for selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [^{35}S]-GTPγS binding measurements, following the addition of nicotinic acid.

P2 membrane preparation - Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at –80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10mM Tris-HCl and 0.1mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000*g* for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000*g* for 30min. P2 particulate fractions were resuspended in buffer A and stored at –80°C until required.

[^{35}S]-GTPγS binding - Assays were performed at room temperature either in 96-well format as described previously (Wieland, T. and Jakobs, K.H. (1994) *Methods Enzymol.* **237**, 3-13) or in an adapted protocol carried out in 384-well format.

96-well format: Briefly, membranes (10 µg per point) were diluted to 0.083 mg/ml in assay buffer (20 mM HEPES, 100 mM NaCl, 10 mM $MgCl_2$, pH7.4) supplemented with saponin (10 mg/l) and pre-incubated with 10 µM GDP. Various concentrations of nicotinic acid or related molecules were added, followed by [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) at 0.3 nM (total vol. of 100 µl) and binding was allowed to proceed at room temperature for 30 min. Non-specific binding was determined by the inclusion of 0.6 mM GTP. Wheatgerm agglutinin SPA beads (Amersham) (0.5 mg) in 25µl assay buffer were added and the whole was incubated at room temperature for 30 min with agitation. Plates were centrifuged at 1500 g for 5 min and bound [^{35}S]-GTPγS was determined by scintillation counting on a Wallac 1450 microbeta Trilux scintillation counter.

384-well format: Briefly, the dilution of standard or test compounds were prepared and added to a 384-well plate in a volume of 10µl. Membranes (HM74A or HM74) were diluted in assay buffer (20mM HEPES, 100mM NaCl, 10mM $MgCl_2$, pH7.4)

supplemented with saponin (60μg/ml), Leadseeker WGA beads (Amersham; 250μg/well) and 10μM GDP, so that the 20μl volume added to each well contains 5μg of membranes. [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) was diluted (1:1500) in assay buffer and 20μl added to each well. Following the addition of the radioligand, the plates were sealed, pulse spun and incubated for 4hours at room temperature. At the end of the incubation period the plates were read on a Leadseeker machine (VIEWLUX PLUS; Perkin-Elmer) to determine the levels of specific binding.

Compounds according to Formula (I) and Formula (Ia) have been synthesised (see synthetic examples below) and tested in the assays discussed above. The compounds have an EC50 of 5.0 or greater and an efficacy of 30% or greater.

In-vivo testing

HM74A agonists are tested in male Spague-Dawley rats (200-250grammes) which have been fasted for at least 12 hours prior to the study. The compounds are dosed intravenously (5ml/kg) or by oral gavage (10ml/kg). Blood samples (0.3ml tail vein bleed) are taken pre-dose and at three times post-dose (times ranging from 15minutes to 8 hours post-dose). Each blood sample is transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000 *g* for 5 minutes) to produce a plasma sample. The plasma samples are assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, is used as a surrogate for HM74A agonist activity.

In order to determine whether compounds of the invention exhibit the flushing response associated with nicotinic acid, they are dosed to anaesthetised guinea-pigs. Nicotinic acid is used as positive control. Male Dunkin Hartley guinea pigs (300-800g) are fasted for 12 hours prior to being anaesthetised with a mixture of Ketamine hydrochloride (Vetalar, 40mg/kg i.m.), Xylazine (Rompun, 8mg/kg i.m.) and sodium pentobarbitone (Sagatal, 30mg/kg i.p.). Following anaesthesia a tracheostomy is performed and the animals are mechanically ventilated with room air (10-12mL/kg, 60 breaths/min). A jugular vein, and a carotid artery, are cannulated for intravenous administration of test compound and collection of blood respectively. An infra-red temperature probe (Extech Instruments) is placed 3-5mm from the tip of the left ear. Temperature measurements are recorded every minute from 5 minutes prior to test compound or nicotinic acid and up to 40 minutes post-administration of test compound or nicotinic acid. Data is automatically collected on a Psion computer before being transferred for data analysis within an Excel spreadsheet. Prior to, and at frequent time points after compound administration, blood samples (0.3ml) are taken via the carotid arterial cannula and transferred to Microtainer (BD) tubes containing lithium heparin. The samples are mixed thoroughly on a blood roller and then stored on ice prior to centrifugation at 1200g for 5 minutes.

As indicated above, compounds of Formula (I) are useful in human or veterinary medicine, in particular as activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

Thus, there is provided as a further aspect of the present invention a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, for use in human or veterinary medicine, particularly in the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with a condition in which under-activation of the HM74A receptor contributes to the condition or in which activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt or solvate thereof.

More particularly, the present invention provides a method for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, or hypertriglyceridaemia which method comprises administering to said human or animal subject an effective amount of a compound of Formula (Ia) or a physiologically acceptable salt or solvate thereof. The invention also provides methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity which methods comprise administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate or derivative thereof.

The amount of a HM74A modulator which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01μg to 1g of a HM74A modulator. Thus ampoules for injection may contain, for example, from 0.01μg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g. No toxicological effects are indicated/expected when a compound of the invention is administered in the above mentioned dosage range.

A compound of the present invention may be employed as the compound *per se* in the treatment of a the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, but is preferably presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the HM74A modulator as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the HM74A modulator.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a HM74A modulator; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active HM74A modulator with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the HM74A modulator optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a

powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a HM74A modulator in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the HM74A modulator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of an HM74A modulator, preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the HM74A modulator with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the HM74A modulator.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit

dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a HM74A modulator with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The HM74A modulator is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2- tetrafluorethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

The compounds of the instant invention may be used in combination with one or more other therapeutic agents for example in combination with other classes of dyslipidaemic drugs e.g. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further aspect, the use of such a combination in the treatment of diseases in which under-activation of the HM74A receptor contributes to the disease or in which activation of the receptor will be beneficial and the use of a compound of Formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof in the manufacture of a medicament for the combination therapy of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, or hypertriglyceridaemia, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity.

When the compounds of the present invention are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent. The combination may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The compounds of the Formula (I) have useful duration of action.

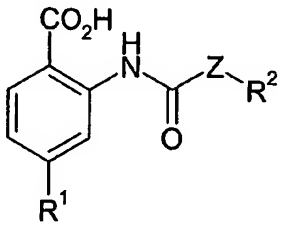
Compounds of Formula (I) and salts and solvates thereof may be prepared by various synthetic routes, including the methodology described hereinafter which constitutes a further aspect of the invention.

Abbreviations

DMSO	Dimethylsulphoxide
DCM	Dichloromethane
THF	Tetrahydrofuran
TFA	Trifluoroacetic Acid
DMF	Dimethylformamide
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
TBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	1-hydroxy benzotriazole
CDI	Carbonyl diimidazole
DIPEA	N,N-diisopropylethylamine
PyHOTs	Pyridinium tosylate

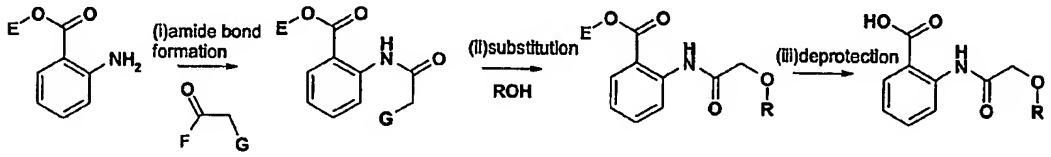
Method A:

A process for preparing compounds of Formula (I)



(I)

in which R^1 represents hydrogen, Z represents -Y-W-X-, Y represents $-(CH_2)_pO-$, p represents the integer 1, and W, X and R^2 are as defined above is set out in scheme (a):



E = protecting group
F = activating group for acyl transfer
G = leaving group
R = W-X-R^2

Scheme (a)

Accordingly, the present invention provides a process for preparing a compound of Formula (I) or of Formula (Ia) comprising:

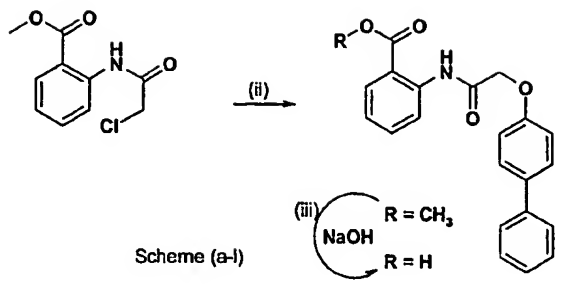
(i) amide bond formation by acetylation of an ester of anthranilic acid (O-protected anthranilic acid);

(ii) addition of W or W-X-R^2 by substitution of a leaving group (G);

(iii) deprotection of the anthranilic acid group;

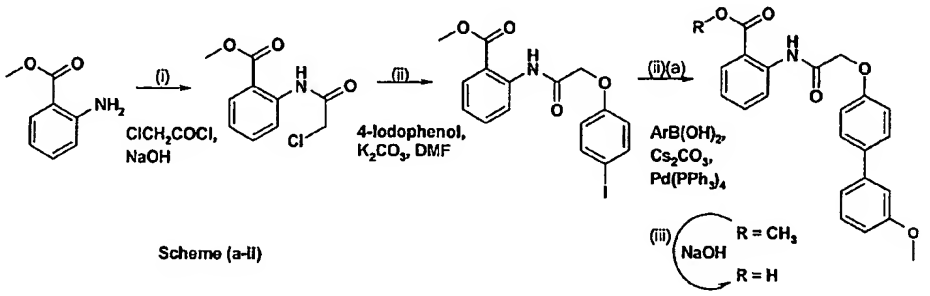
and where desired or necessary converting a resultant free acid or base compound of Formula (I) or of Formula (Ia) into a physiologically acceptable salt form, or vice versa, or converting one salt form into another physiologically acceptable salt form.

A particular example of a process according to Method A is set out in scheme (a-i), which illustrates steps (ii) and (iii) of the method:



Scheme (a-I)

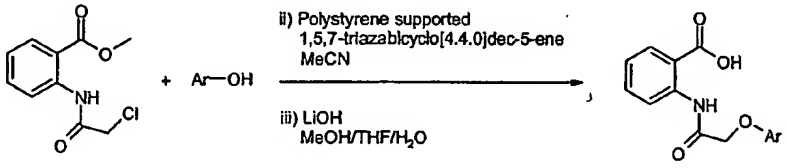
Another particular example of a process according to Method A is a process for preparing compounds of the invention in which Z represents -Y-W-X-, Y represents $-(CH_2)_pO-$, p represents the integer 1, X is absent, whilst W and R^2 are as defined above, is set out in scheme (a-ii):



Scheme (a-II)

in which step (ii) comprises addition of W and a further step (ii)(a), addition of R^2, is included in the form of a further substitution reaction.

A variation of steps (ii) and (iii) of Method A may be used to prepare compounds of the invention in which Z represents $-(CH_2)_nO-$, n is 1 and R^2 represents aryl, and is set out in scheme (a-iii).

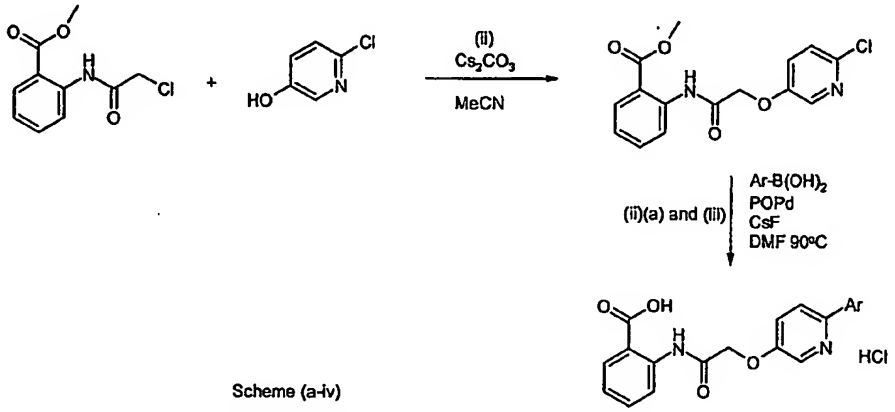


Scheme (a-III)

ii) Alkylation of aromatic alcohol with methyl 2-[(chloroacetyl)amino]benzoate (protected anthranilic acid)

iii) Hydrolysis of methyl ester using lithium hydroxide (deprotection).

A further variation of steps (ii) and (iii) of Method A, set out in scheme (a-iv), may be used to prepare compounds in which Z is Y-W-X, Y is $-(CH_2)_pO-$, p represents the integer 1 and W is heteroaryl:



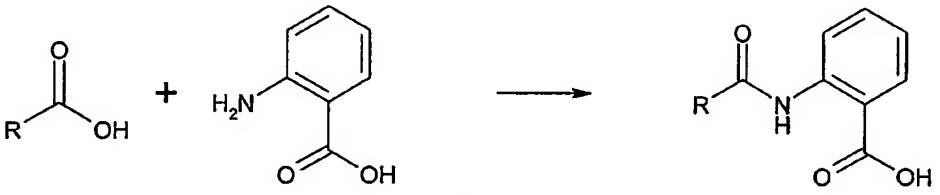
Scheme (a-iv)

ii) Alkylation of 6-chloro-3-pyridinol with methyl 2-[(chloroacetyl)amino]benzoate using caesium carbonate as base

iii) Suzuki coupling of chloropyridine with aromatic boronic acid (addition of R^2) and hydrolysis of methyl ester (deprotection).

Method B

A process for the preparation of compounds of the invention is set out in scheme (b)



Scheme (b)

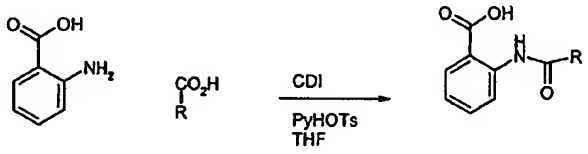
wherein R represents $-Z-R^2$ as defined above.

Accordingly, the present invention provides a process for preparing a compound of Formula (I) or of Formula (Ia) comprising:

(i) formation of an amide between the amine group of anthranilic acid (2-amino-benzoic acid) and an activated acyl transfer reagent derived from a carboxylic acid

(ii) where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

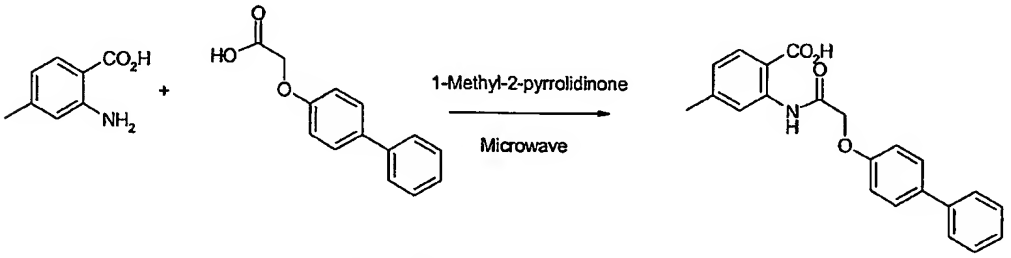
A particular example of a process according to Method B is set out in scheme (b-i)



Scheme (b-I)

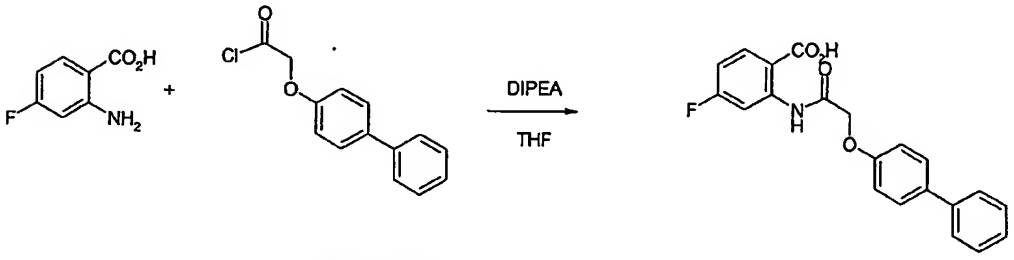
a) Coupling of anthranilic acid with a carboxylic acid using carbonyl diimidazole (CDI)

Further particular examples of alternative conditions useful in Method B, are given in schemes (b-ii), (b-iii) and (b-iv):



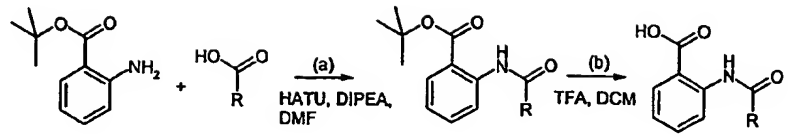
Scheme (b-II)

a) Coupling of substituted anthranilic acid with (4-biphenylyloxy)acetic acid in microwave



Scheme (b-III)

a) Coupling of substituted anthranilic acid with (4-biphenylyloxy)acetyl chloride

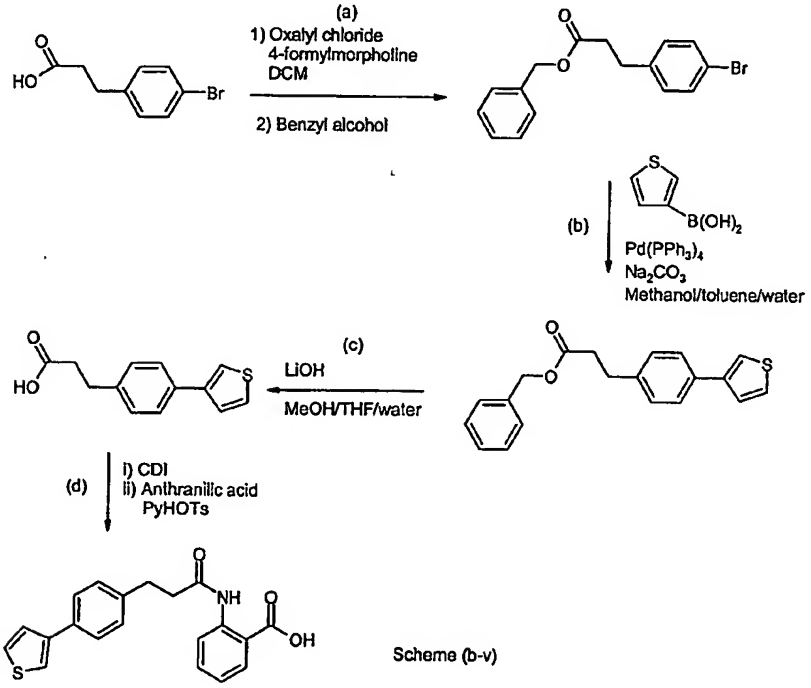


Scheme (b-iv)

a) Amide coupling of anthranilic acid with a carboxylic acid

b) Removal of *tert*-butyl ester with TFA (deprotection)

A further example of a process according to Method B, for preparation of compounds in which Z is Y-W-X is set out below as step (d) of scheme (b-v). Steps (a) to (c) of scheme (b-v) produce the R-CO_2H starting material of scheme (b) above.



Scheme (b-v)

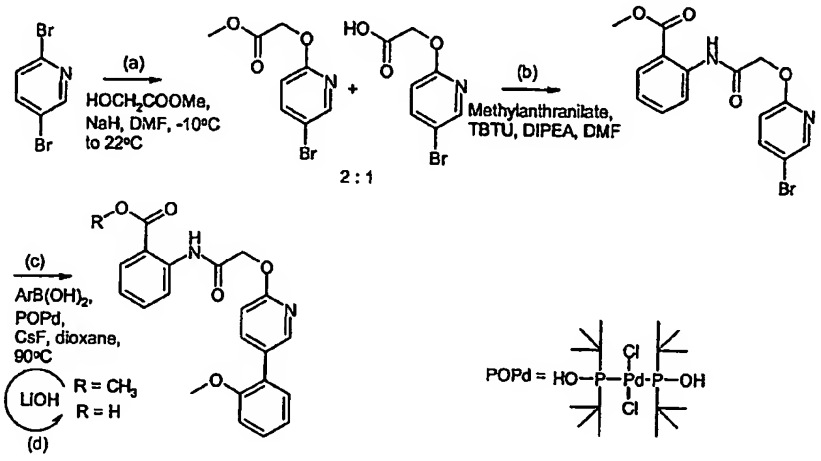
a) Formation of the benzyl ester (protecting group)

b) Suzuki coupling with 3-thiophene boronic acid (adding in R^2)

c) Base hydrolysis of benzyl ester (deprotection)

d) Amide coupling with anthranilic acid, using CDI, to obtain the compound of Formula (I).

A variation of the scheme (b-v) example of Method B, which may be used for the preparation of compounds in which Z is Y-W-X and W is heteroaryl, is set out below in scheme (b-vi)



Scheme (b-vi)

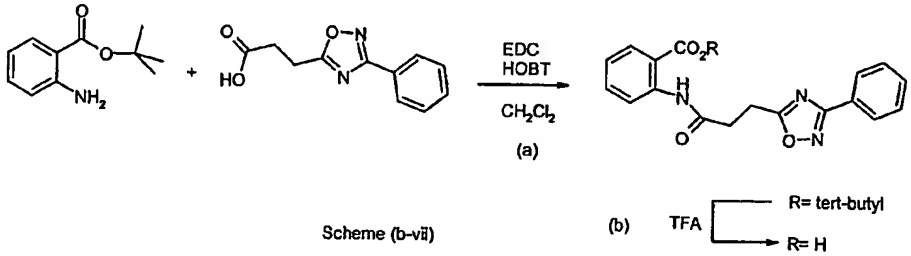
a) nucleophilic displacement of bromide and partial hydrolysis of methyl ester

b) amide coupling with anthranilic acid methyl ester

c) Suzuki coupling to add R^2

d) Base-catalysed hydrolysis of the methyl ester (deprotection)

A further variation which may be employed when W is heteroaryl, especially oxadizolyl, is given in scheme (b-vii):



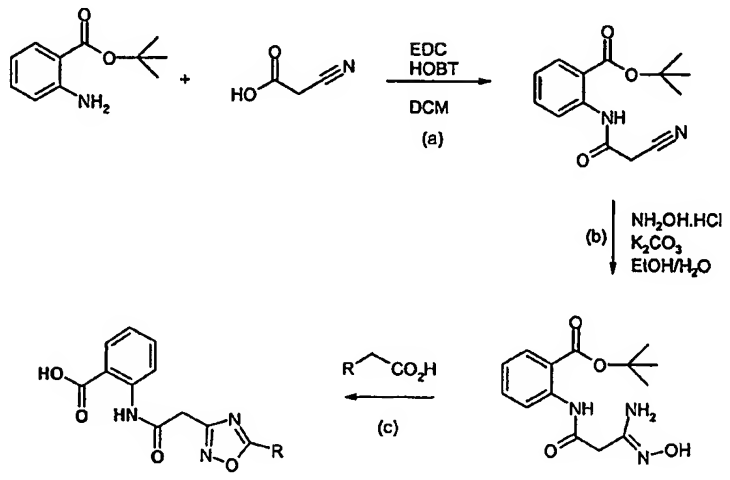
Scheme (b-vii)

a) Coupling of 1,1-dimethylethyl 2-aminobenzoate with the carboxylic acid using EDC/HOBT

b) Removal of the tert-butyl ester using TFA (deprotection).

Method C

A process for preparing compounds of the present invention in which W is oxadizolyl and X represents for example $-(CH_2)_q-$, $-(CH_2)_pO-$ or $-(CH_2)_pS-$ is given in scheme (c).

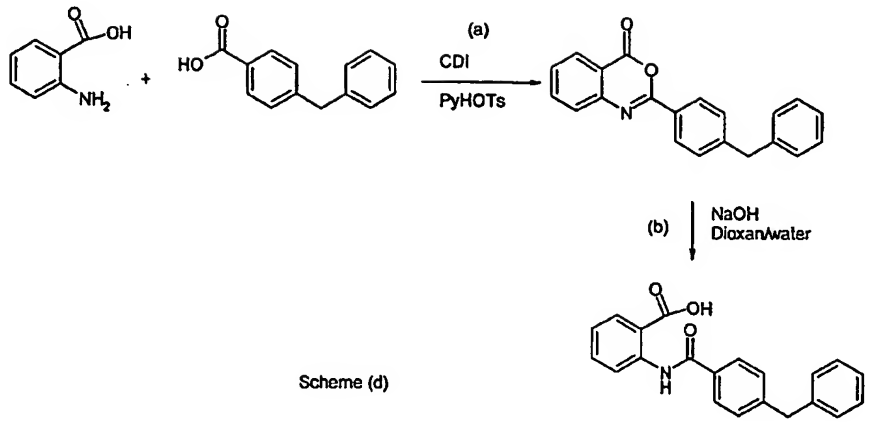


Scheme (c)

a) Amide coupling of 1,1-dimethylethyl 2-aminobenzoate with the carboxylic acid using EDC/HOBT
b) Reaction of the nitrile with hydroxylamine
c) Cyclisation with carboxylic acid in which R represents X-R^2 and deprotection to form a compound of the invention.

Method D

A further process for preparing compounds of the present invention is given in scheme (d):



Scheme (d)

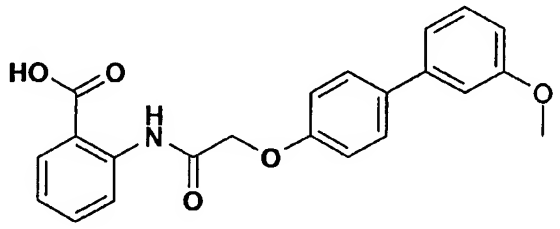
a) Coupling of anthranilic acid with aromatic acid and cyclisation of amide onto acid
b) Hydrolysis of cyclic product to free carboxylic acid

The following non-limiting examples illustrate the present invention:

Synthetic Examples:

A. Example compounds synthesised using Method A

Example 1: 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid



a) 2-(2-Chloro-ethanoylamino)-benzoic acid methyl ester

Methyl anthranilate (0.85 ml, 6.6 mmole, 1 equiv) and chloroacetyl chloride (0.63 ml, 7.9 mmole, 1.2 equiv) were stirred vigorously in a mixture of THF (10 ml) and water (10 ml) and cooled to 4°C while a 2M solution of NaOH (3.3 ml) was slowly added. After 0.5 hours, the reaction mixture was extracted twice with ethyl acetate and the organic solution was washed with brine, dried with magnesium sulphate and evaporated to dryness. The resulting solid (1.5 g) was triturated with two aliquots of hexane to give the title compound as a white solid (1.15 g, 76%); δ_H (400MHz, $CDCl_3$) 3.96 (3H, s), 4.21 (2H, s), 7.34 (1H, dd, J = 1.2 and 7.6 Hz), 7.58 (1H, dd, J = 1.6 and

7.6 Hz), 8.07 (1H, dd, J = 1.6 and 8 Hz), 8.65 (1H, dd, J = 1.2 and 8.8 Hz); m/z 250.0 [MNa^+].

b) 2-[2-(4-Iodo-phenoxy)-ethanoylamino]-benzoic acid methyl ester ,

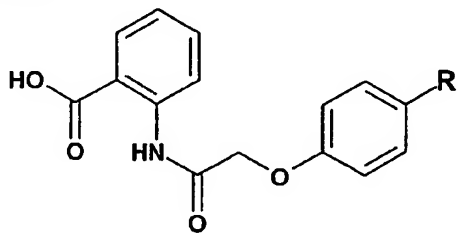
2-(2-Chloro-ethanoylamino)-benzoic acid methyl ester **2** (0.5 g, 2.2 mmole,1 equiv), K_2CO_3 (0.46 g, 3.3 mmole,1.5 equiv), and 4-iodophenol (0.58 g, 2.64 mmole,1.2 equiv) were heated together in DMF (10 ml) at 90°C for 6 hr. The solvent was evaporated and the residue crystallised from t-butylmethyl ether to yield the title compound (480 mg, 53%); δ_H (400MHz, CD_3OD) 3.95 (3H, s), 4.68 (2H, s), 6.94 – 6.98 (2H, m), 7.20 (1H, dt, J = 1.1 and 7.7 Hz), 7.65 (1H, dt, J = 1.7 and 7.3 Hz), 7.63 – 7.67 (2H, m), 8.09 (1H, J = 1.6 and 8.1 Hz), 8.71 (1H, dd, J = 0.9 and 8.4 Hz); m/z 412.0 [MH^+], 434.0 [MNa+].

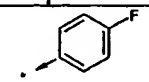
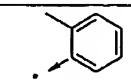
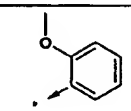
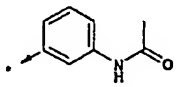
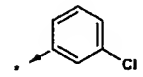
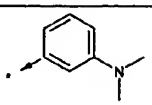
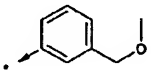
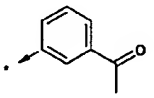
c) 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid,

3-Methoxyphenylboronic acid (44.4 mg, 0.29 mmole, 1.2 equiv), Cs_2CO_3 (325 mg, 1 mmole, 4 equiv) and 2-[2-(4-Iodo-phenoxy)ethanoylamino]-benzoic acid methyl ester (100 mg, 0.24 mmole, 1 equiv) were dissolved in THF / water (5/1, 25 ml) and degassed by bubbling a stream of argon through the solution for 25 minutes. Tetrakistriphenylphosphine palladium (5.8 mg, 0.005 mmole, 0.02equiv) was added and the reaction mixture was heated for 18 hours at 80°C under an atmosphere of argon.

The reaction mixture was treated with ethanol (5 ml) and water (5 ml), basified with 2M NaOH and heated to reflux for 4 hours. After cooling, the reaction mixture was acidified with HCl and extracted twice with ethyl acetate. The combined extracts were dried with magnesium sulphate and evaporated to dryness. The crude solid (66 mg) was chromatographed over a column of silica 60 eluting with DCM / MeOH (9 : 1) to give the product 2-[2-(3'-Methoxy-biphenyl-4-yloxy)-ethanoylamino]-benzoic acid as a white solid (44 mgs, 40%); δ_H (400MHz, DMSO-d6) 3.81 (3H, s), 4.75 (2H, s), 6.89 (1H, dd, J = 0.8 and 8 Hz), 7.10-7.20 (5H, m), 7.34 (1H, t, J = 8 Hz), 7.51 (1H, br t), 7.64 (2H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.65 (1H, d, J = 8 Hz); m/z 378.2 [MH^+].

The following compounds of Examples 2-9 were also prepared using the Method of Example 1:



Example No:	Compound: R =	yield	m/z
2		8 mg 13%	366.1
3		6.7 mg 11%	362.2
4		7.5 mg 12%	378.1
5		2.1 mg 3%	405.1
6		6.1 mg 12%	382.2
7		9.1 mg 14%	391.2
8		4.2 mg 6.6%	392.2
9		4.9 mg 7.7%	390.1

Example 2: δ_H (400MHz, DMSO-d6) 4.78 (2H, s), 7.10 -7.32 (5H, m), 7.55 – 7.73 (5H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.71 (1H, dd, J = 3.7 and 8.4 Hz), 12.13 – 12.29 (1H, m), 13.50 – 13.90 (1H, br s).

Example 3: δ_H (400MHz, CD_3OD) 2.23 (3H, s), 4.72 (2H, s), 7.15-7.30 (9H, m), 7.57 (1H, dd, J = 8 and 1.2 Hz), 8.11 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz).

Example 4: δ_H (400MHz, DMSO-d6) 3.76 (3H, s), 4.78 (2H, s), 7.01 (1H, t, J = 7.4 Hz), 7.08 – 7.14 (3H, m), 7.26 (1H, t, J = 7.3 Hz), 7.27 – 7.36 (2H, m), 7.44 – 7.47 (2H, m), 7.60 – 7.66 (1H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.72 (1H, dd, J = 1.6 and 8.4 Hz),

Example 5: δ_H (400MHz, DMSO-d6) 2.06 (3H, s), 4.78 (2H, s), 7.17 -7.20 (3H, m), 7.25 – 7.30 (1H, m), 7.35 (1H, t, J = 8.0 Hz), 7.50 – 7.53 (1H, m), 7.56 – 7.64 (3H, m), 7.83 – 7.85 (1H,m), 8.02 (1H, d, J = 8 Hz), 8.70 (1H, d, J = 8.0 Hz),

Example 6: δ_H (400MHz, DMSO-d6) 4.80 (2H, s), 7.17 -7.20 (3H, m), 7.37 – 7.41 (1H, m), 7.47 (1H, t, J = 8.0 Hz), 7.56 – 7.75 (5H, m), 8.03 (1H, dd, J = 1.6 and 8.0 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.25 (1H, s), 13.60 – 14.00 (1H, br s).

Example 7: δ_H (400MHz, DMSO-d6) 2.97 (6H, s), 4.79 (2H, s), 6.74 - 6.77 (1H, m), 6.94 – 7.00 (2H, m), 7.12 – 7.29 (4H, m), 7.62 – 7.67 (3H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.20 (1H, s).

Example 8: δ_H (400MHz, DMSO-d6) 3.32 (3H, s), 4.47 (2H, s), 4.79 (2H, s), 7.16 -7.23 (3H, m), 7.27 (1H, d, J = 7.6 Hz), 7.42 (1H, t, J = 8.0 Hz), 7.54 – 7.56 (2H, m), 7.64 – 7.67 (3H, m), 8.03 (1H, dd, J = 1.6 and 8 Hz), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.25 (1H, s), 13.60 – 13.90 (1H, br s).

Example 9: δ_H (400MHz, DMSO-d6) 3.65 (3H, s), 4.81 (2H, s), 7.18 - 7.23 (3H, m), 7.58 – 7.65 (2H, m), 7.74 (2H, m), 7.89 – 7.93 (2H, m), 8.04 (1H, dd, J = 1.6 and 8 Hz), 8.15 – 8.16 (1H, m), 8.72 (1H, dd, J = 0.8 and 8.4 Hz), 12.24 (1H, s), 13.50 – 14.00 (1H, br s).

Example 10: 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid

a) 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid methyl ester

Methyl (2-chloroacetyl)anthranilate (0.5 g, 2.2 mmole, 1 equiv), 4-phenylphenol (0.45 g, 2.64 mmole, 1.2 equiv) and potassium carbonate (0.456 g, 3.3 mmole, 1.5 equiv) were heated to 90°C in DMF (10 ml) for 6 hours. The solvent was removed by evaporation and the residue was chromatographed over a column of silica 60 eluting with DCM to give the title compound as a white solid (460 mg, 58%); δ_H (400MHz, DMSO-d6) 3.91 (3H, s), 4.80 (2H, s), 7.20 (2H, d, J = 8.8 Hz), 7.22-7.27 (1H, m), 7.30 – 7.36 (1H, m), 7.44 (2H, t, J = 8.0 Hz), 7. 60 – 7.70 (5H, m), 8.02 (1H, dd, J = 1.2 and 8 Hz), 8.64 (1H, d, J = 8 Hz); m/z 362.1 [MH^+], 384.1 [MNa^+].

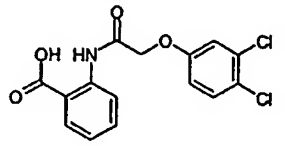
b) 2-[2-(Biphenyl-4-yloxy)-ethanoylamino]-benzoic acid

Methyl (4-phenylphenoxy)acetylanthranilate (153 mg, 0.42 mmole, 1 equiv) was dissolved in a mixture of water and ethanol (2 : 1, 10 ml) and the solution was heated to reflux with 2M NaOH solution (0.23 ml, 0.46 mmole, 1.1 equiv) overnight. The product was twice extracted from the cooled reaction mixture with ethyl acetate and the combined extracts were evaporated to give a crude product (146 mg) which was chromatographed over silica 60 eluting with DCM / MeOH (10 : 1) to give the title compound (35 mg, 24%); δ_H (400MHz, DMSO-d6 / D_2O) 4.74 (2H, s), 7.16 (1H, t, J = 7.8 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.33 (1H, t, J = 7.3 Hz), 7.45 (2H, t, J = 7.8 Hz), 7. 52 (1H, dd, J = 1.4 and 8.5 Hz), 7.63 (4H, t, J = 8.3 Hz), 8.05 (1H, d, J = 6.9 Hz), 8.61 (1H, d, J = 8.2 Hz); m/z 348.1 [MH^+], 370.1 [MNa^+].

Example 11: 2-[2-(3-Bromo-phenoxy)-ethanoyl amino]-benzoic acid

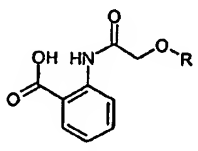
δ_H (400MHz, DMSO-d6) 4.78 (2H, s), 7.12 (1H, dd), 7.18 - 7.22 (2H, m), 7.30 – 7.34 (2H, m), 7.65 (1H, t), 8.03 (1H, d), 8.71 (1H, d), 12.17 (1H, d), m/z

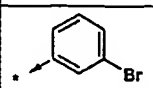
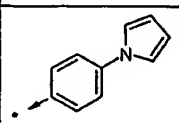
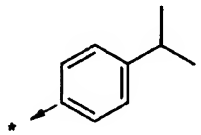
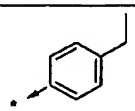
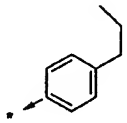
Example 12: 2-({[(3,4-dichlorophenyl)oxy]acetyl}amino)benzoic acid



Polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene [Fluka AG, crosslinked with 2% 1,4-divinylbenzene, loading 2.6 mmol/g] (0.115g, 0.3mmol) was treated with a solution of 3,4-dichlorophenol (0.048g, 0.15mmol) in acetonitrile (0.5ml). After 1 hour the mixture was treated with a solution of methyl 2-[(chloroacetyl)amino]benzoate (Journal of Heterocyclic Chemistry 1989, 26(6), 1807-1810) (0.029g, 0.13mmol) in acetonitrile (0.5ml) and then heated at 45°C for 18 hours. The cooled mixture was filtered and the resin washed with a further 4ml of acetonitrile. The filtrate and washings were combined, evaporated to dryness and the residue treated with a solution of lithium hydroxide (0.011g, 0.45 mmol) in a mixture of methanol (0.42 ml), water (0.42 ml) and THF (0.17 ml). The mixture was stirred and heated to 45°C for 2 hours then stirred at ambient temperature for 18 hours. The mixture was acidified to about pH4 by the addition of 2M aqueous hydrochloric acid and the precipitated product filtered and dried to afford the title compound (0.0106g, 25%) as a white solid. NMR δ_H (400MHz, d^6-DMSO) 4.80 (s, 2H), 7.11 (dd, 1H, J=2.8, 8.8Hz), 7.20 (t, 1H, J=7.8Hz), 7.38 (d, 1H, J=3.0Hz), 7.62 (d, 2H, J=8.8Hz), 8.03, (dd, 1H, J=1.5, 8.1Hz), 8.68 (d, 1H, J=8.3Hz), 12.20 (bs, 1H), one exchangeable proton not observed to δ_H 13; m/z 340,342 [MH^+]; HPLC rt: 3.86 mins.

The following compound examples 13-17 were also prepared using method A



Example No:	Compound: R =	yield	m/z
13		5.4mg (10.3%)	350, 352 [MH^+]
14		4.7mg (9.3%)	337 [MH^+]
15		5.2mg (11%)	314 [MH^+]
16		9.8mg (21.8%)	300 [MH^+]
17		10.1mg (21.4%)	314 [MH^+]

Example 13: 2-({[(3-bromophenyl)oxy]acetyl}amino)benzoic acid
NMR δ_H (400MHz, d^6-DMSO) 4.77 (s, 2H), 7.11 (dd, 1H, J=2.3, 8.3Hz), 7.16-7.24 (m, 2H), 7.26-7.38 (m, 2H), 7.63 (dt, 1H, J=1.2, 7.1Hz), 8.03 (dd, 1H, J=1.5, 7.8Hz), 8.69 (d, 1H, J=8.3Hz), 12.24 (s, 1H), one exchangeable proton not observed to δ_H 13.

Example 14: 2-[({[4-(1*H*-pyrrol-1-yl)phenyl]oxy}acetyl)amino]benzoic acid
NMR δ_H (400MHz, d^6-DMSO) 4.77(s, 2H), 6.23(t, 2H, J=2.0Hz), 7.17(d, 2H, J=9.1Hz), 7.20(t, 1H, J=7.3Hz), 7.27(t, 2H, J=2.0Hz), 7.54(d, 2H, J=8.8Hz), 7.63(dt, 1H, J=1.5, 7.1Hz), 8.03(dd, 1H, J=1.5, 7.8Hz), 8.70(d, 1H, J=8.1Hz), both exchangeable protons not observed to δ_H 13.

Example 15: 2-[({[4-(1-methylethyl)phenyl]oxy}acetyl)amino]benzoic acid
NMR δ_H (400MHz, d^6-DMSO) 1.17(d, 6H, J=6.8Hz), 2.85(m, 1H), 4.70(s, 2H), 7.01(d. 2H, J=8.6Hz), 7.18 – 7.22(m, 3H), 7.64(t, 1H, J=8.6Hz), 8.03(dd, 1H, J=1.5, 8.1Hz), 8.71(d, 1H, J=8.1Hz), 12.18(s, 1H), one exchangeable proton not observed to δ_H 13.

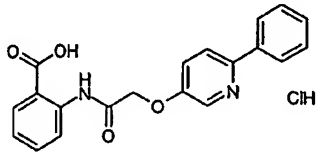
Example 16: 2-({[(4-ethylphenyl)oxy]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 1.14 (t, 3H, J=7.6Hz), 2.54 (q, 2H, J=7.6Hz), 4.67 (s, 2H), 6.99 (d, 2H, J=8.6Hz), 7.14-7.18 (m, 3H), 7.60 (dd, 1H, J=1.5, 7.1Hz), 8.01 (dd, 1H, J=1.5, 7.8Hz), 8.68 (d, 1H, J=8.3Hz), 12.34 (br s, 1H), one exchangeable proton not observed to δ_H 13.

Example 17: 2-({[(4-propylphenyl)oxy]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 0.87 (t, 3H, J=7.32Hz), 1.50-1.60 (m, 2H), 2.47-2.51 (m, 2H, partially obscured by DMSO) , 4.69 (s, 2H), 6.99 (d, 2H, J=8.6Hz), 7.15 (d, 2H, J=8.6Hz), 7.19 (t, 1H, J=7.3Hz), 7.63 (dt, 1H, J=1.5, 7.3Hz), 8.02 (d, 1H, J=1.5, 7.8Hz), 8.70 (d, 1H, J=8.6Hz), 12.19 (s, 1H), 13.80 (br s, 1H).

Example 18: 2-({[(6-phenyl-3-pyridinyl)oxy]acetyl}amino)benzoic acid hydrochloride



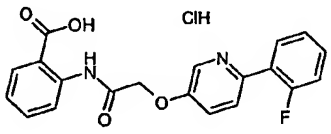
a) Methyl 2-({[(6-chloro-3-pyridinyl)oxy]acetyl}amino)benzoate

A solution of 6-chloro-3-pyridinol (1.71g, 13.2mmol) in 60ml of acetonitrile was treated with caesium carbonate (8.6g, 26.9mmol) and the mixture was subsequently stirred for 15 minutes. Methyl 2-[(chloroacetyl)amino]benzoate (3g, 13.2mmol) was added portionwise over 5 minutes followed by approximately 20ml of acetonitrile to facilitate the stirring. The mixture was stirred for 6 hours, allowed to stand overnight and then evaporated to dryness. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with further ethyl acetate and the combined organic extracts were dried over magnesium sulfate, filtered and evaporated to dryness. The product was recrystallized from methanol to yield the title compound as a white solid (4.1g, 97%); NMR δ_H (400MHz, $CDCl_3$) 3.94 (s, 3H), 4.68 (s, 2H), 7.16 (dt, 1H, J=1.0, 7.5 Hz), 7.31 (d, 1H, J=8.8 Hz), 7.38 (dd, 1H, J=3.0, 8.8 Hz), 7.58 (dt, 1H, J=1.5, 8.5 Hz), 7.38 (dd, 1H, J=1.3, 8.0 Hz), 8.28 (d, 1H, J=3.0 Hz); 8.28 (d, 1H, J=3.0 Hz), 8.77 (d, 1H, J=8.5 Hz); m/z 321 [MH^+]

b) 2-({[(6-phenyl-3-pyridinyl)oxy]acetyl}amino)benzoic acid hydrochloride

A mixture of methyl 2-({[(6-chloro-3-pyridinyl)oxy]acetyl}amino)benzoate (0.02g, 0.063 mmol), caesium fluoride (0.029g, 0.191mmol) and phenylboronic acid (0.01g, 0.082mmol) in 0.5ml of dimethoxyethane under an atmosphere of nitrogen was treated with dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(2-) (POPd) (0.0006g, 0.0012mmol) and heated at 90°C for 18 hours. The mixture was cooled, treated with additional phenylboronic acid (0.004g, 0.026mmol) and then heated at 90°C for a further 18 hours. The cooled mixture was then treated with a solution of potassium carbonate (0.02g, 0.14 mmol) in water (0.4 ml) and then heated at 90°C for 6 hours and cooled. The mixture was cautiously acidified to pH 1 with 2M aqueous hydrochloric acid, evaporated to dryness and the product purified using mass-directed HPLC to yield the title compound as a pale yellow solid. (0.0042g, 19%) NMR δ_H (400MHz, d^6-DMSO) 4.90(s, 2H), 7.18(dt, 1H, J=1.0, 7.1Hz), 7.39(t, 1H, J=7.3Hz), 7.47(t, 2H, J=7.8Hz), 7.58-7.63(m, 2H), 7.97(d, 1H, J=8.8Hz), 8.03(m, 3H), 8.53(d, 1H, J=2.8Hz), 8.68(d, 1H, J=7.6Hz), 12.45(br s, 1H), one exchangeable proton not observed to δ_H 13; m/z 349 [MH^+].

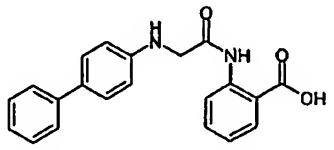
Example 19: 2-[({[6-(2-fluorophenyl)-3-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride



Prepared using method A to afford the title compound 2.9 mg (8%). NMR δ_H (400MHz, d^6-DMSO) 4.90(s, 2H), 7.18(t, 1H, J=7.8Hz), 7.30-7.34(m, 2H), 7.42-7.48(m, 1H), 7.58-7.63(m, 2H), 7.80(d, 1H, J=8.8Hz), 7.90(dt, 1H, J=1.5, 7.8Hz), 8.03(d, 1H, J=7.8Hz), 8.58(d, 1H, J=2.8Hz), 8.67(d, 1H, J=8.3Hz), 12.58(br s, 1H), one exchangeable proton not observed up to δ_H 13; m/z 367.1 [MH^+]; HPLC rt 3.46 mins.

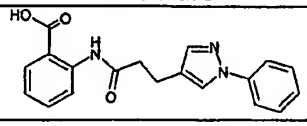
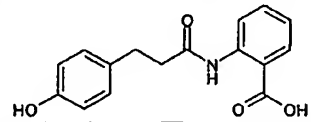
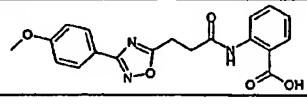
B. Example compounds synthesised using Method B

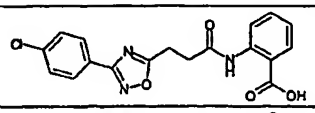
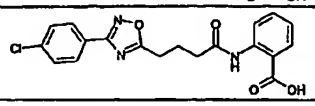
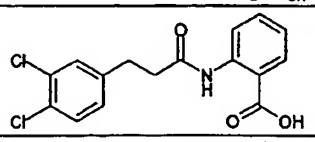
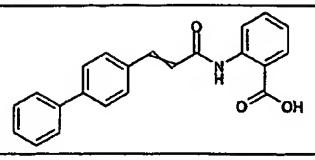
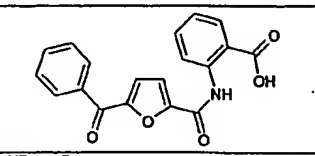
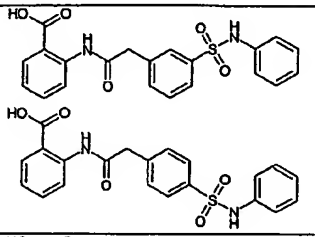
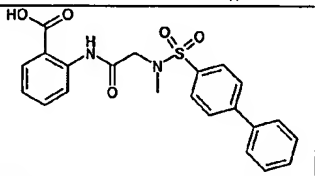
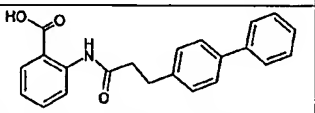
Example 20: 2-[(*N*-4-biphenylylglycyl)amino]benzoic acid



A stirred solution of the TFA salt of N-4-biphenylylglycine (204mg, 0.60mmol, 1.0equiv)(US (1987) US4656185 A 19870407 CAN107:154159 AN 1987:554159 CAPLUS) and CDI (107mg, 0.66mmol, 1.1equiv) in anhydrous THF (10ml) was left to react at rt. for 60 minutes. Anthranilic acid (98mg, 0.72mmole, 1.2equiv) and pyridinium *p*-toluenesulfonate (361mg, 1.43mmole, 2.4equiv) were added and the mixture heated at gentle reflux for 16 hours. The mixture was allowed to cool, filtered and the filtrate concentrated. The residue was partitioned between EtOAc and water. The organic fraction was separated, washed with 0.5M HCl(aq), then dried over magnesium sulfate and concentrated. The residue was taken up into MeOH and passed down an amino-propyl ion-exchange column (10g), eluting with 5% AcOH/MeOH. The appropriate product fractions were combined and concentrated. The resulting residue was washed with CH_3CN and pure product precipitated out and collected by filtration, then dried under vacuum to give an off-white solid (35mg, 17%). δH (400MHz, d^6-DMSO) 3.88 (2H, d, J=5.5Hz), 6.68 (3H, app. d; J=8.5Hz), 7.11 (1H, dd, J=1.1 and 7.5Hz), 7.22 (1H, app. t, J=7.6Hz), 7.36 (2H, app. t, J=7.6Hz), 7.44 (2H, app. d, J=8.5Hz), 7.54 (2H, app. d, J=7.3Hz), 7.58 (1H, app. t, J=7.8Hz), 7.94 (1H, dd, J=1.7 and 7.9Hz), 8.72 (1H, d, J=8.0Hz), 12.19 (1H, br. s), 13.58 (1H, v.br. s); m/z 347.2 [MH^+].

The following compound examples 21-31 were also prepared using Method B

Example	Structure	LCMS [M-H^+]
21		334.04
22		283.94
23		365.97

24		370.20
25		383.41
26		337.91
27		343.88
28		334.28
29*		409.44
30		426.00[M+H$^+$]
31		344.41

* Acetic acids purchased as a mixture of isomers

Propionic acids for preparation of examples 21-31 are commercially available or known compounds.

Selected NMR data:

Example 21:

δ_H (400MHz, DMSO-d6) 2.74 (2H, t), 2.84 (2H, t), 7.14(1H, t), 7.27 (1H, t), 7.46 (2H,t), 7.58 (1H, t), 7.63 (1H, s), 7.75 (2H, d), 7.96 (1H, d), 8.33 (1H, s), 8.50 (1H, d), 11.16 (1H, br.s), 13.30 (1H, br.s); m/z 334.04 [M-H$^+$].

Example 22:

δ_H (400MHz, MeOH) 2.65 (2H, t), 2.92 (2H, t), 6.68 (2H, d), 7.05 (2H, d), 7.12 (1H, br.s), 7.51 (1H, t), 8.06 (1H, br.s), 8.54 (1H, d);
m/z 283.97 [M-H$^+$].

Example 23:
δ_H (400MHz, DMSO-d6) 3.03 (2H, t), 3.27 (2H, t), 3.83 (3H, s), 7.08 (2H, d), 7.14 (1H, t), 7.56 (1H, t), 7.92 (2H, d), 7.98 (1H, d), 8.41 (1H, d), 11.30 (1H, br.s), 13.55 (1H, br.s); m/z 365.97 [M-H$^+$].

Example 24:
δ_H (400MHz, DMSO-d6) 3.05 (2H, t), 3.31 (2H, t), 7.13 (1H, t), 7.57 (1H, t), 7.63 (2H, d), 7.98 (3H, m), 8.40 (1H, d), 11.30 (1H, br.s), 13.55 (1H, br.s); m/z 370.20 [M-H$^+$].

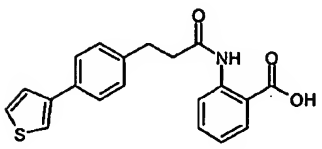
Example 25:
δ_H (400MHz, DMSO-d6) 2.14 (2H, m), 2.58 (2H, t), 3.10 (2H, t), 7.11 (1H, t), 7.55 (1H, t), 7.63 (2H, d), 7.95 (1H, d), 7.98 (2H, d), 8.43 (1H, d), 11.15 (1H, br.s), 13.40 (1H, br.s); m/z 383.41 [M-H$^+$].

Example 26:
δ_H (400MHz, DMSO-d6) 2.75 (2H, t), 2.94 (2H, t), 7.13 (1H, t), 7.29 (1H, d), 7.52 (1H, d), 7.56 (2H, m), 7.96 (1H, d), 8.44 (1H, d), 11.11 (1H, br.s), 13.35 (1H, br.s); m/z 337.91 [M-H$^+$].

Example 27:
δ_H (400MHz, DMSO-d6) 6.92 (1H, d), 7.18 (1H, t), 7.40 (1H, t), 7.50 (2H, t), 7.62 (1H, t), 7.68 (1H, d), 7.74 (4H, m), 7.83 (2H, m), 8.03 (1H, d), 8.60 (1H, d), 11.45 (1H, br.s); m/z 343.88 [M-H$^+$].

Example 30:
δ_H (400MHz, DMSO-d6) 2.90 (3H, s), 3.90 (2H, s), 7.19 (1H, t), 7.45 (1H, m), 7.51 (2H, t), 7.60 (1H, t), 7.75 (2H, d), 7.93 (4H, s), 8.02 (1H, d), 8.59 (1H, d), 12.00 (1H, br.s); m/z 425.00 [M+H$^+$].

Example 31: 2-({3-[4-(3-thienyl)phenyl]propanoyl}amino)benzoic acid



a) Phenylmethyl 3-(4-bromophenyl)propanoate

4-Formylmorpholine (1 drop) was added to a stirred solution of 3-(4-bromophenyl)propanoic acid (5.0g, 21.8mmole, 1.0equiv) and oxalyl chloride (3.81ml, 43.7mmole, 2.1equiv) in DCM (30ml) under nitrogen at rt. When gas evolution ceased the volatiles were evaporated and the residue taken up in DCM (30ml). Benzyl alcohol (2.26ml, 21.8mmole, 1.0equiv) was added in one portion and stirring continued under nitrogen for 2 hours. The volatiles were evaporated and the residue partitioned between DCM (50ml) and saturated $NaHCO_3$ (aq) (50ml). The organic phase was separated and the aqueous phase washed with DCM (2 x 50ml). The organic phases were combined, dried over magnesium sulfate and the solvent evaporated. The product was purified by column chromatography (20% Et_2O: PE) on silica gel providing a colourless oil (6.08g, 87%). δ_H (400MHz, $CDCl_3$) 2.65 (2H, t, J=7.6Hz), 2.92 (2H, t, J=7.5Hz), 5.10 (2H, s), 7.05 (2H, d, J=8.3Hz), 7.25-7.40 (7H, m); m/z 336.4, 338.4 [MNH_4^+]

b) Phenylmethyl 3-[4-(3-thienyl)phenyl]propanoate

A flask was charged, under an atmosphere of nitrogen, with $Pd(PPh_3)_4$ (29mg, 0.025mmole, 0.04equiv), phenylmethyl 3-(4-bromophenyl)propanoate (200mg, 0.63mmole, 1.0equiv) and toluene (4ml). To this was added 2M Na_2CO_3 (aq) (2ml) and a solution of 3-thiophene boronic acid (152mg, 1.19mmole, 1.9equiv) in EtOH (1ml). The mixture was heated at 90°C for 5 hours. After cooling, the mixture was partitioned between 1M HCl (aq) and EtOAc. The organic layer was separated then washed with brine, dried over magnesium sulfate, and concentrated, yielding a dark brown solid. The crude product was purified by passing down an SPE (5g) cartridge eluting with EtOAc/ cyclohexane mixtures (5%-80% EtOAc). The product fractions were concentrated to afford a pale pink solid (208mg, quant. ca.90% pure). δH (400MHz, $CDCl_3$) 2.72 (2H, t, J=7.7Hz), 3.00 (2H, t, J=7.8Hz), 5.13 (2H, s), 7.23 (2H, d, J=8.1Hz), 7.30-7.44 (8H, m), 7.52 (2H, d, J=7.8Hz). m/z 323.1 [MH^+], 340.2 [MNH_4^+].

c) 3-[4-(3-thienyl)phenyl]propanoic acid

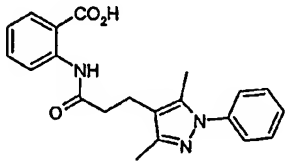
A stirred solution of phenylmethyl 3-[4-(3-thienyl)phenyl]propanoate (147mg, 0.46mmole) in MeOH (5ml) was treated with a solution of LiOH (44mg) in water (0.3ml) then left to stir at rt. for 18 hours. The mixture was partitioned between 2M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried over

magnesium sulfate and concentrated, giving a beige solid. The solid was taken up into MeOH and passed down an amino-propyl column (5g). The product was eluted with 10% AcOH/ MeOH then concentrated to give the product as an off-white solid (64mg, 60%). δ_H (400MHz, d^6-DMSO) 2.55 (2H, t, J=7.7Hz), 2.83 (2H, t, J=7.5Hz), 7.26 (2H, d, J=8.3Hz), 7.52 (1H, dd, J=1.4 and 5.2Hz), 7.62 (3H, m), 7.81 (1H, dd, J=1.3 and 2.8Hz), 12.17 (1H, br. s). m/z 231.1 $[M-H]^-$.

d) 2-({3-[4-(3-thienyl)phenyl]propanoyl}amino)benzoic acid

A stirred solution of 3-[4-(3-thienyl)phenyl]propanoic acid (64mg, 0.28mmol, 1.0equiv) and CDI (49mg, 0.30mmol, 1.1equiv) in anhydrous THF (4ml) was left to react at rt. for 40 minutes. Anthranilic acid (45mg, 0.33mmole, 1.2equiv) and pyridinium *p*-toluenesulfonate (166mg, 0.66mmole, 2.4equiv) were added and the mixture heated at gentle reflux for 18 hours. The mixture was allowed to cool, filtered and the filtrate concentrated. MeOH was added and the product collected by filtration and then dried to give a white solid (15mg, 15%). δH (400MHz, d^6-DMSO) 2.74 (2H, t, J=7.7Hz), 2.96 (2H, t, J=7.4Hz), 7.14 (1H, t, J=7.5Hz), 7.30 (2H, d, J=8.0Hz), 7.52-7.64 (5H, m), 7.81 (1H, m), 7.97 (1H, dd, J=1.2 and 7.9Hz), 8.48 (1H, d, J=8.3Hz), 11.17 (1H, s), 13.63 (1H, br. s); m/z 352.1 $[MH^+]$.

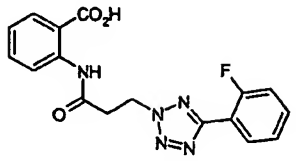
Example 32: 2-{[3-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)propanoyl]amino} benzoic acid



Prepared using Method B to yield the title compound (22mg, 9%).

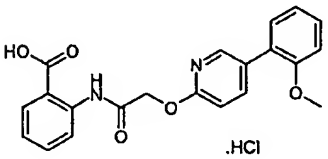
NMR δ_H (400MHz, d^6-DMSO) 2.16 (3H, s), 2.21 (3H, s), 2.53 (2H, t, J=8Hz), 2.74 (2H, t, 8Hz), 7.12 (1H, app t, J=8Hz), 7.3-7.5 (5H, m), 7.57 (1H, d, app t, J=8 and 2Hz), 7.96 (1H, dd, J=8 and 2Hz), 8.5 (1H, d, J=8Hz), 11.3 (1H, s), one exchangeable proton not observed to δ_H 13. m/z 364 $[MH^+]$

Example 33: 2-({3-[5-(2-fluorophenyl)-2*H*-tetrazol-2-yl]propanoyl}amino)benzoic acid



To 3-[5-(2-fluorophenyl)-2*H*-tetrazol-2-yl]propanoic acid (115mg, 0.66mmol) in THF (5ml) was added carbonyl diimidazole (110mg, 0.68mmol) and the solution stirred for 1h. Anthranilic acid (90mg, 0.66mmol) was added to the solution followed by pyridine tosylate (410mg, 1.64mmol). The mixture was heated at 70°C for 18h, cooled, filtered and concentrated. Chromatography (3:2 cyclohexane/ethyl acetate as eluent) over silica yielded product that was further purified by autoprep hplc (gradient elution: water + 30 to 85%acetonitrile + 0.05% formic acid) to provide product as a white solid (32mg, 14%). NMR δ_H (400MHz, d^6-DMSO) 3.25 (2H, t, J=6 Hz), 5.05 (2H, t, J=6 Hz), 7.15 (1H, t, 8Hz), 7.4 (2H, m), 7.6 (2H, m), 7.97 (1H, dd, J=8 and 2 Hz), 8.02 (1H, d, app t, J=8 and 2 Hz), 8.38 (1H, d, J=8 Hz), 11.15 (1H, s), 13.6 (1H, br s). m/z 356 [MH^+].

Example 34: 2-{[({5-[2-(methyloxy)phenyl]-2-pyridinyl}oxy)acetyl]amino}benzoic acid hydrochloride



a) Methyl [(5-bromo-2-pyridinyl)oxy]acetate and [(5-bromo-2-pyridinyl)oxy]acetic acid, 2:1 mixture

2,5-dibromopyridine (10g, 42.2mmol, 1equiv) was stirred vigorously in DMF and cooled to –10°C (salted ice bath) and NaH (60% suspension in mineral oil, 2.6g, 65.0mmol, 1.5equiv) was added in five portions. Methyl glycolate (1.8ml, 46.6mmol, 1.1equiv) was added dropwise, and the reaction mixture allowed to warm to room temperature for 16 hr under an atmosphere of nitrogen. The organic solution was poured onto brine, then extracted three times with ethyl acetate, dried with magnesium sulfate and evaporated to dryness to give crude methyl [(5-bromo-2-pyridinyl)oxy]acetate (7.6g, 73%) as a brown solid; LC/MS : m/z 246.3 [MH^+]. The brine solution was acidified with cHCl and extracted three times with ethyl acetate,

dried with magnesium sulfate and evaporated to dryness to give crude [(5-bromo-2-pyridinyl)oxy]acetic acid (2.5 g, 26%) as a brown solid; m/z 232.0 [MH^+].

b) methyl 2-({[(5-bromo-2-pyridinyl)oxy]acetyl}amino)benzoate

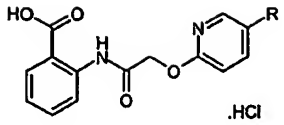
To a solution of crude [(5-bromo-2-pyridinyl)oxy]acetic acid (5.0g, 21.6mmol, 1equiv), and DIPEA (4.2ml, 24.2mmol, 1.1equiv) in DMF (80ml) was added methyl anthranilate (5.6 ml, 43.6mmol, 2equiv) and solution of TBTU (7.1g, 22.1mmol, 1equiv) in DMF (20ml), and the mixture stirred for 96 hr under an atmosphere of nitrogen. The reaction mixture was concentrated under reduced pressure then partitioned between chloroform and 2N HCl. The separated organic phase was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulphate and concentrated under reduced pressure to afford a brown solid which was purified by Biotage™ chromatography (90g, Si) (eluting with cyclohexane/ethyl acetate 4:1), then triturated with cold ether and filtered to give the title compound (2g, 26%) as a white solid;: LC/MS : m/z 367.0 $[M+H]^+$.

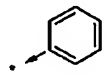
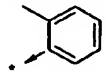
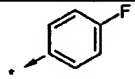
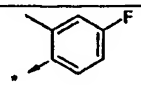
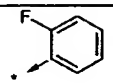
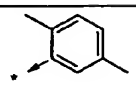
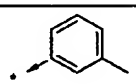
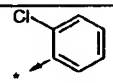
b) 2-[({[5-(2-methoxyphenyl)-2-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride

[2-(methyloxy)phenyl]boronic acid (0.023 , 0.15mmol, 1.5 equiv), CsF (0.046g, 0.3mmol, 3equiv), and methyl 2-({[(5-bromo-2-pyridinyl)oxy]acetyl}amino)benzoate (0.036g, 0.1mmol, 1equiv) and dihydrogen dichlorobis(di-tert-butylphosphinito-kP)palladate(2-) (0.001g, 2umol, 2mol%) were dissolved in anhydrous dioxane and heated for 16 hr at 90°C under an atmosphere of nitrogen.

The reaction mixture was treated with water (1ml) and K_2CO_3 (0.040g, 0.3mmol, 3equiv) and heated at 90°C for 4 hr. After cooling, the reaction mixture was acidified with 2N HCl and the resulting solid filtered then purified by preparative h.p.l.c. to afford the title compound as a cream solid (0.007 g, 20%); δ_H (400MHz, d^6-DMSO): 12.19 (1H, br s), 8.67 (1H, d, J=8 Hz), 8.24 (1H, d, J=2 Hz), 7.99 (1H, dd, J=1.5 and 8 Hz), 7.94 (1H, dd, J=2 and 9 Hz), 7.60 (1H, t, J=8 Hz), 7.38–7.30 (2H, m), 7.18–7.01 (4H, m), 4.99 (2H, s), 3.77 (3H, s), one exchangeable proton not observed to δ_H 13; LC/MS: m/z 379.2 [MH^+], Rt 3.56 min.

Similarly the following compounds of Examples 35-42 were prepared using Method B as described in Ex. 34, but with purification step via preparative h.p.l.c. preceding the hydrolysis step:



Example No:	Compound: R =	yield	m/z
35		2.9 mg 17%	349.1 [MH$^+$]
36		1.5 mg 4%	363.0 [MH$^+$]
37		1.1mg 3%	367.0 [MH$^+$]
38		0.4 mg 1%	380.9 [MH$^+$]
39		3 mg 8%	366.9 [MH$^+$]
40		1.8 mg 5%	377.0 [MH$^+$]
41		15.8 mg 44%	362.9 [MH$^+$]
42		8.5 mg 22%	382.8 [MH$^+$]

Example 35:

2-({[(5-phenyl-2-pyridinyl)oxy]acetyl}amino)benzoic acid hydrochloride

NMR δ_H (400MHz, d^6-DMSO) 5.00 (2H, s), 7.11 (1H, d, J=8.6 Hz), 7.16 (1H, t, J=7.6 Hz), 7.37 (1H, t, J=7.6 Hz), 7.47 (2H, t, J=7.8 Hz), 7.60 (1H, td, J=8.6 and 1.5 Hz), 7.67 (2H, dd, J=8.6 and 1.3 Hz), 7.98 (1H, d, J=7.8 Hz), 8.13 (1H, dd, J=8.6 and 2.5 Hz), 8.49 (1H, d, J=2.5 Hz), 8.67 (1H, d, J=8.3 Hz), 12.18 (1H, br s), one exchangeable proton not observed to δ_H 13.

Example 36:

2-[({[5-(2-methylphenyl)-2-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride

NMR : δ_H (400MHz, d^6-DMSO) 2.22 (3H, s), 5.00, (2H, s), 7.09 (1H, d, J=8.6 Hz), 7.16–7.32 (5H, m), 7.62 (1H, td, J=8.6 and 1.5Hz), 7.85 (1H, dd, J=8.6 and 2.5 Hz), 8.00 (1H, dd, J=7.8 and 1.8 Hz), 8.14 (1H, d, J=2.5 Hz), 8.69 (1H, d, J=8.3 Hz), 12.08 (1H, br s), 13.80 (1H, br s).

Example 37:

2-[({[5-(4-fluorophenyl)-2-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride

NMR δ_H (400MHz, d^6-DMSO), 4.99 (2H, s), 7.10 (1H, d, J=8.6 Hz), 7.16 (1H, t, J=7.3 Hz), 7.28 -7.30 (2H, m), 7.61 (1H, t, J=7.3 Hz), 7.70-7.74 (2H, m), 7.98 (1H, dd, J=8.1 and 1.5 Hz), 8.12 (1H, dd, J=8.6 and 2.5 Hz), 8.47 (1H, d, J=2.3 Hz), 8.68 (1H, d, J=8.3 Hz), 12.07 (1H, br s), 13.79 (1H, br s)

Example 40:

2-[({[5-(2,5-dimethylphenyl)-2-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride

NMR δ_H (400MHz, d^6-DMSO), 2.16 (3H, s), 2.28 (3H, s), 5.00 (2H, s), 7.03-7.09 (3H, m), 7.16-7.19 (2H, m), 7.63 (1H, td, J=8.6, and 1.5 Hz), 7.83 (1H, dd, J=8.6 and 2.5 Hz), 7.99 (1H, dd, J=8.1 and 1.5 Hz), 8.12 (1H, d, J=2.0 Hz), 8.69 (1H, d, J=8.1 Hz), 12.02 (1H, br s), 13.79 (1H, br s)

Example 41:

2-[({[5-(3-methylphenyl)pyridin-2-yl]oxy}acetyl)amino]benzoic acid hydrochloride

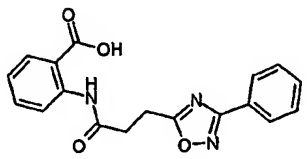
NMR δ_H (400MHz, d^6-DMSO) 13.78 (1H, br s), 12.04 (1H, br s), 8.68 (1H, d, J=8 Hz), 8.46 (1H, d, J=2 Hz), 8.12 (1H, dd, J=2 and 9 Hz), 7.98 (1H, dd, J=1.5 and 8 Hz), 7.62 (1H, td, J=8 and 2 Hz), 7.48–7.44 (2H, m), 7.35 (1H, t, J=8 Hz), 7.20 – 7.17 (2H, m), 7.09 (1H, d, J=9 Hz), 5.00 (2H, s), 2.36 (3H, s).

Example 42:

2-[({[5-(2-chlorophenyl)-2-pyridinyl]oxy}acetyl)amino]benzoic acid hydrochloride

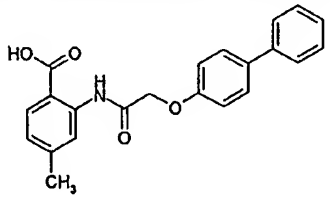
NMR δ_H (400MHz, d^6-DMSO) 12.13 (1H, br s), 8.68 (1H, d, J=8 Hz), 8.22 (1H, d, J=2 Hz), 7.99 (1H, dd, J=1.5 and 8 Hz), 7.95 (1H, dd, J=2 and 8.5 Hz), 7.64–7.58 (2H, m), 7.46–7.42 (3H, m), 7.17 (1H, td, J=7.5 and 1 Hz), 7.11 (1H, d, J=8.5 Hz), 5.01 (2H, s), one exchangeable proton not observed to δ_H 13.

Example 43: 2-{[3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanoyl]amino}benzoic acid



A solution of 3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanoic acid (0.1g, 0.46mmol) in dichloromethane (10ml) was treated with 1,1-dimethylethyl 2-aminobenzoate (0.089g, 0.46mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.097g, 0.51mmol) and 1*H*-1,2,3-benzotriazol-1-ol (0.075g, 0.56mmol). After 4 days the reaction mixture was evaporated to dryness and the residue treated with a solution of trifluoroacetic acid (1ml) in dichloromethane (1ml). After 2 hours the mixture was evaporated to dryness and the residue dissolved in 1ml of DMSO and subjected to purification using mass-directed HPLC. The title compound, which crystallized as a white solid from the eluant upon standing for 2 days, was filtered and dried to give 0.024g (15%) of the title compound. NMR. δ_H (400MHz, d^6-DMSO); 3.05(t, 2H, J=7.0 Hz), 3.32(t, 2H, J=6.8 Hz, (partially obscured by water), 7.15(t, 1H, J=7.5 Hz), 7.56(m, 4H), 7.98(m, 3H), 8.41(d, 1H, J=8.3 Hz), 11.27(s, 1H), 13.67(s, 1H); m/z 338 [MH^+].

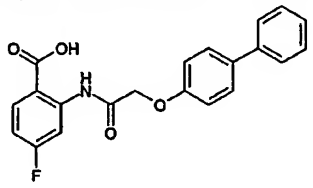
Example 44: 2-{[(4-Biphenylyloxy)acetyl]amino}-4-methylbenzoic acid



A mixture of 2-amino-4-methylbenzoic acid, (37.3mg, 0.25mmole, 1 equiv), (4-biphenylyloxy)acetic acid (56.2mg, 0.25mmole, 1 equiv) and 1-methyl-2-pyrrolidinone (50 ul, 0.5umole, 0.002 equiv) were heated in a CEM Discover Focussed microwave system (200W, 10 min, 200°C). Acetonitrile (4ml) was added and the product was purified by HPLC. Column, Supercosil ABZ+Plus 10x2.12cm; Flow, 4ml/min; Gradient, 30% acetonitrile + 0.05% formic acid / 70% water + 0.1% formic acid to 60% organic phase over 20 mins then 60% organic for 10 mins. To give the title compound as an off white solid (4mg, 4%); δ_H (400MHz, d^6-DMSO) 2.37 (3H, s), 4.77 (2H, s), 7.0 (1H, d J=8.5 Hz), 7.17 (2H, d, J=9 Hz), 7.32 (1H, t, J=7.5 Hz), 7.44 (2H, t, J=8 Hz),

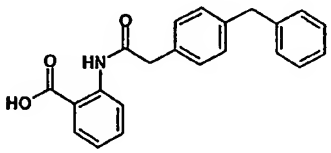
7.64 (4H, app t, J=9 Hz), 7.91 (1H d, J=8 Hz), 8.55 (1H, s), 12.39 (1H, v br s), 13.68 (1H, v br s); m/z 362.2 [MH^+].

Example 45: 2-{[(4-Biphenylyloxy)acetyl]amino}-4-fluorobenzoic acid



To a solution of 2-amino-4-fluorobenzoic acid (46.5mg, 0.3mmol, 1equiv.) in tetrahydrofuran (1ml) was added a solution of (4-biphenylyloxy)acetyl chloride (74mg, 0.3mmol, 1 equiv.) in tetrahydrofuran (1ml) and diisopropylethylamine (0.48g, 3.7mmol, 12.3equiv.). The solution was stirred for 17 hours under nitrogen and then evaporated under reduced pressure. The crude product was purified by mass directed HPLC to give the title compound (76mg, 69%); δ_H (400MHz, d^6-DMSO) 4.81 (2H, s), 7.05 (1H, m), 7.18 (2H, m), 7.33 (1H, m), 7.43 (2H, m), 7.57-7.70 (4H, m), 8.11 (1H, m), 8.53 (1H, d, J=12 Hz), 12.46 (1H, br s), CO_2H not observed to δ_H 13; m/z 366 [MH^+], Rt 4.09 min

Example 46: 1,1-dimethylethyl 2-({[4-(phenylmethyl)phenyl]acetyl}amino)benzoate

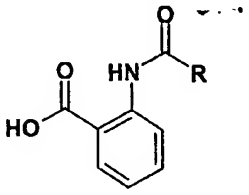


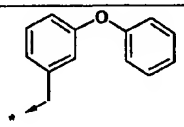
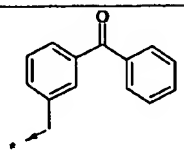
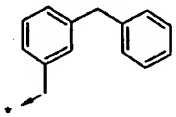
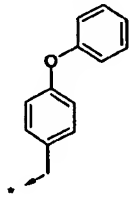
a) 1,1-dimethylethyl 2-({[4-(phenylmethyl)phenyl]acetyl}amino)benzoate

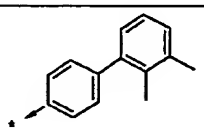
To a solution of [4-(phenylmethyl)phenyl]acetic acid (0.059g, 0.26mmol, 1equiv) and DIPEA (0.054ml, 0.31mmol, 1.2equiv) in anhydrous DMF (0.5ml) was added a solution of HATU (0.119g, 0.31mmol, 1.2equiv) in DMF (0.5ml), followed by 1,1-dimethylethyl 2-aminobenzoate (0.060 g, 0.31mmol, 1.2equiv) in DMF (0.5ml). The mixture was stirred under an atmosphere of nitrogen for 72 hr, then concentrated under reduced pressure and partitioned between DCM and 2N HCl. The separated organic phase was washed with saturated sodium bicarbonate then evaporated under a stream of nitrogen and purified by preparative h.p.l.c. to give the title compound (0.033g, 32%) as a white solid; LC/MS : m/z 402.2 $[MH]^+$.

b) 2-({[4-(phenylmethyl)phenyl]acetyl}amino)benzoic acid 1,1-dimethylethyl 2-({[4-(phenylmethyl)phenyl]acetyl}amino)benzoate (0.033g, 0.08mmol, 1equiv) was shaken in a mixture of TFA (0.8ml) and DCM (1.0ml) for 4 hr then concentrated under a stream of nitrogen to give the title compound (0.028g, 100%) as a white solid; δ_H (d^6-DMSO) 3.69 (2H, s), 3.92 (2H, s), 7.20 - 7.29 (10H, m), 7.56 (1H, td, J=8.6 and 1.5 Hz), 7.94 (1H, dd, J=7.8 and 1.8 Hz), 8.46 (1H, d, J=8.3Hz), 11.15 (1H, s), 13.60 (1H, br s); LC/MS: m/z 346.2 $[MH]^+$.

Similarly the following compounds of Examples 47-51 were prepared using Method B, but ABW-SPE was employed after the amide coupling step in the workup of Examples 32-39 (eluting with methanol):



Example No:	Compound: R =	yield	m/z
47		38.0mg 100%	348.3 $[MH^+]$
48		39.8mg 90%	360.3 $[MH^+]$
49		38.0mg 100%	346.2 $[MH^+]$
50		5.4mg 89%	348.3 $[MH^+]$

Example No:	Compound: R =	yield	m/z
51		42.7mg 78%	346.2 [MH^+]

Example 47

2-{[(3-phenoxyphenyl)acetyl]amino}benzoic acid

δ_H (400MHz, d^4-MeOD) 8.55 (1H, d, J=8 Hz), 8.04 (1H, dd, J=8 and 1Hz), 7.52 (1H, td, J=8 and 1.5Hz), 7.35–7.29 (3H, m), 7.14–7.07 (3H, m), 7.01–6.99 (3H, m), 6.89 (1H, dd, J=8 and 2Hz), 3.73 (2H, s), both exchangeable protons not observed to δ_H 13.

Example 48

2-({[3-(phenylcarbonyl)phenyl]acetyl}amino)benzoic acid

δ_H (400MHz, d^4-MeOD) 8.56 (1H, d, J=8.5 Hz), 8.05 (1H, dd, J=8 and 1.5Hz), 7.80-7.68 (10H, m), 7.31 (1H, td, J=7 and 1Hz), 5.48 (2H, s), both exchangeable protons not observed to δ_H 13.

Example 49

2-({[3-(phenylmethyl)phenyl]acetyl}amino)benzoic acid

δ_H (400MHz, d^4-MeOD) 8.53 (1H, d, J=8 Hz), 8.04 (1H, d, J=8 Hz), 7.51 (1H, t, J=8 Hz), 7.27-7.08 (10H, m), 3.96 (2H, s), 3.70 (2H, s) both exchangeable protons not observed to δ_H 13.

Example 50

2-{[(4-phenoxyphenyl)acetyl]amino}benzoic acid

δ_H (400MHz, d^6-DMSO) 11.25 (1H, br s), 8.50 (1H, d, J=8 Hz), 7.95 (1H, dd, J=8 and 1.5Hz), 7.56 (1H, td, J=7.5 and 1.5Hz), 7.40-7.36 (4H, m), 7.13 (2H, t, J=8 Hz), 7.02–6.98 (4H, m), 3.75 (2H, s), one exchangeable proton not observed to δ_H 13.

Example 51

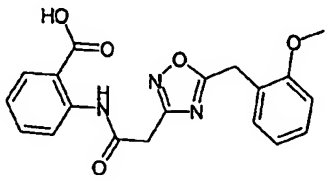
2-{[(2',3'-dimethyl-4-biphenylyl)carbonyl]amino}benzoic acid

δ_H (400MHz, d^6-DMSO) 2.13 (3H, s), 2.31 (3H, s), 7.08 (1H, d, J=7.3Hz), 7.17 (1H, t, J=7.6 Hz), 7.20-7.25 (2H, m), 7.52 (2H, d, J=8.3 Hz), 7.69 (1H, t, J=7.1 Hz), 8.02 (2H, d, J=8.1 Hz), 8.08 (1H, d, J=7.8 Hz), 8.75 (1H, d, J=7.8 Hz), 11.80 (1H, br s), 12.25 (1H, s).

C. Example Compounds Synthesised Using Method C.

Example 52:

2-{[(5-{[2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)acetyl]amino}benzoic acid



a) 1,1-dimethylethyl 2-[(cyanoacetyl)amino]benzoate

A solution of 1,1-dimethylethyl 2-aminobenzoate (5g, 25.9mmol) in dichloromethane (60ml) was treated with cyanoacetic acid (2.2g, 25.9mmol), 1H-1,2,3-benzotriazol-1-ol (4.2g, 31.1mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.5g, 28.6mmol). The mixture was stirred for 18 hours and then evaporated to dryness. The residue was partitioned between ethyl acetate (150ml) and saturated aqueous sodium bicarbonate (150ml). The aqueous phase was extracted with ethyl acetate (150ml) and the organic fractions were combined, dried over magnesium sulfate, filtered and evaporated to yield the crude title compound (6.8g, 100%) as a light brown solid. m/z 278 [MNH_4^+].

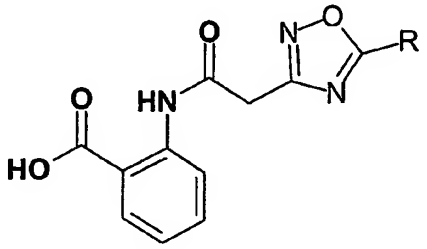
b) 1,1-dimethylethyl 2-{[(3Z)-3-(hydroxyamino)-3-iminopropanoyl]amino}benzoate

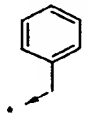
To a suspension of 1,1-dimethylethyl 2-[(cyanoacetyl)amino]benzoate (6.8g, 25.9mmol) in a mixture of ethanol (60ml) and water (20ml) was added potassium carbonate (6g, 43.5mmol) and hydroxylamine hydrochloride (2.6g, 37.4mmol). The mixture was heated at 100°C for 4 hours then cooled and evaporated to dryness. The residue was partitioned between ethyl acetate (250ml) and saturated aqueous sodium bicarbonate (150ml). The aqueous phase was extracted with further ethyl acetate (100ml) and the organic fractions were combined, dried over magnesium sulfate, filtered and evaporated. The product was purified by chromatography using KP Sil™ silica (32-63um, 60A, 90g) and eluting using a gradient from ethyl acetate/cyclohexane @ 2:1 to ethyl acetate and then to ethyl acetate/methanol @ 19:1. Evaporation of the desired fractions revealed the title compound (4.9g, 65%) as a white solid. m/z 294 [MH^+].

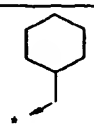
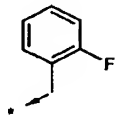
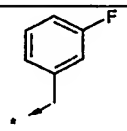
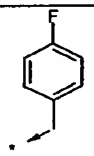
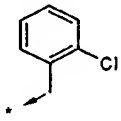
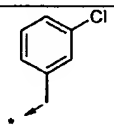
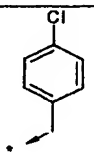
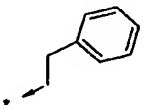
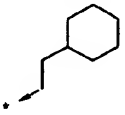
c) 2-({[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

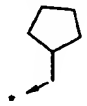
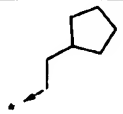
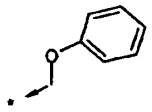
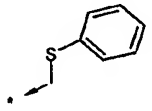
A solution of [2-(methyloxy)phenyl]acetic acid (0.025g, 0.15mmol) in DMF (0.2ml) was treated with ethyl[bis(1-methylethyl)]amine (0.09ml, 0.52mmol) and a solution of a mixture of N-[1*H*-1,2,3-benzotriazol-1-yl(dimethylamino)methylidene]-N-methylmethanaminium tetrafluoroborate (0.033g, 0.1mmol) and 1H-1,2,3-benzotriazol-1-ol (0.03g, 0.02mmol) in DMF (0.2ml). The mixture was stirred for 5 minutes and then treated with a solution of 1,1-dimethylethyl 2-{[(3Z)-3-(hydroxyamino)-3-iminopropanoyl]amino}benzoate (0.03g, 0.1mmol) in DMF (0.2 ml) and stirred at ambient temperature for 1.5 hours, then at 115°C for 4 hours then cooled and evaporated to dryness. The residue was treated with a solution of trifluoroacetic acid (0.5ml) in dichloromethane (0.5ml). After 2 hours, the mixture was evaporated to dryness, the residue dissolved in DMSO (0.5ml) and the product purified using mass-directed HPLC. This yielded the title compound (0.0034g, 9%) as a white solid. NMR δ_H (400MHz, d^6-DMSO) 3.71(s, 3H), 3.95(s, 2H), 4.24(s, 2H), 6.93(t, 1H, J=7.3 Hz), 7.01(d, 1H, J=8.1 Hz), 7.15(t, 1H, J=7.3 Hz), 7.26-7.33(m, 2H), 7.56(t, 1H, J=8.3 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=8.3 Hz), 11.61(s, 1H), one exchangeable proton not observed to δ_H 13; m/z 368 [MH^+].

The following examples 53-66 were prepared in a method analogous to that for 2-{[(5-{[2-(methyloxy)phenyl]methyl}-1,2,4-oxadiazol-3-yl)acetyl]amino}benzoic acid (example 52) using Method C:



Example No:	Compound: R =	yield	m/z
53		2.1mg (6.2%	338 [MH^+]

Example No:	Compound: R =	yield	m/z
54		1.9mg (5.5%)	344 [MH$^+$]
55		3.8mg (10.7%)	356 [MH$^+$];
56		2.1mg (5.9%)	356 [MH$^+$]
57		6.2mg (17.4%)	356 [MH$^+$]
58		3.8mg (10.2%)	372 [MH$^+$]
59		2.1mg (5.6%)	372 [MH$^+$]
60		6.2mg (16.7%)	372 [MH$^+$]
61		11.6mg (33%)	352 [MH$^+$]
62		0.8mg (2.2%)	358 [MH$^+$]

Example No:	Compound: R =	yield	m/z
63		5.9mg (17.9%)	330 [MH^+]
64		8.1mg (23.5%)	344 [MH^+]
65		8.0mg (22.6%)	354 [MH^+]
66		4.3mg (11.6%)	370 [MH^+]

Analytical data

Example 53:

2-({[5-(phenylmethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO), 3.97(s, 2H), 4.36(s, 2H), 7.14(t, 1H, J=7.0 Hz), 7.23-7.34(m, 1H), 7.30-7.41(m, 4H), 7.54(t, 1H, J=7.0 Hz), 7.97(dd, 1H, J=8.0, 1.3 Hz), 8.40(d, 1H, J=8.3 Hz), both exchangeable protons not observed to δ_H 13.

Example 54:

2-({[5-(cyclohexylmethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, $CDCl_3$), 0.95-1.21(m, 6H), 1.60-1.74(m, 4H), 1.91(m, 1H), 2.84(d, 2H, J=7.3 Hz), 4.16(s, 2H), 7.07(t, 1H, J=7.6 Hz), 7.51(dd, 1H, J=8.3, 1.3 Hz), 8.05(dd, 1H, J=8.1, 1.3 Hz), 8.66(d, 1H, J=8.3 Hz), 11.60(s, 1H), one exchangeable proton not observed to δ_H 13.

Example 55:

2-[({5-[(2-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 3.99(s, 2H), 4.41(s, 2H), 7.14-7.26(m, 3H), 7.33-7.44(m, 1H), 7.46(t, 1H, J=7.8 Hz), 7.59(t, 1H, J=7.0 Hz), 7.98(dd, 1H, J=8.0, 1.5 Hz), 8.40(d, 1H, J=8.3 Hz), 11.36(s, 1H), one exchangeable proton not observed to δ_H 13.

Example 56:

2-[({5-[(3-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 4.00(s, 2H), 4.41(s, 2H), 7.17(m, 4H), 7.40(m, 1H,), 7.58(dd, 1H, J=8.5, 1.5 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=8.5 Hz), 11.37(bs, 1H), one exchangeable proton not observed to δ_H 13.

Example 57:

2-[({5-[(4-fluorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 3.99(s, 2H), 4.37(s, 2H), 7.18(m, 3H), 7.40(m, 2H), 7.59(dt, 1H, J=7.3, 1.5 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=8.3 Hz), 11.31(bs, 1H), 13.71(bs, 1H).

Example 58:

2-[({5-[(2-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO 3.99(s, 2H), 4.47(s, 2H), 7.17(dd, 1H, J=6.8, 1.0 Hz), 7.36(m, 2H), 7.50(m, 2H), 7.59(dd, 1H, J=7.1, 1.5 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=8.3 Hz), 11.34(bs, 1H), 13.68(bs, 1H).

Example 59:

2-[({5-[(3-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 4.00(s, 2H), 4.41(s, 2H), 7.17(t, 1H, J=6.8 Hz), 7.21-7.41(m, 3H), 7.46(s, 1H), 7.59(dt, 1H, J=7.3, 1.5 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=8.3 Hz), 11.32(s, 1H), 13.70(s, 1H).

Example 60:

2-[({5-[(4-chlorophenyl)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 3.99(s, 2H), 4.39(s, 2H), 7.17(dd, 1H, J=8.1, 1.3 Hz), 7.35-7.45(m, 4H), 7.58(dt, 1H, J=7.1, 1.5 Hz), 7.97(dd, 1H, J=7.8, 1.5 Hz), 8.40(d, 1H, J=7.8 Hz), 11.41(s, 1H), 13.69(s, 1H).

Example 61:

2-({[5-(2-phenylethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 3.06(t, 2H, J=8.1 Hz), 3.25(t, 2H, J=8.1 Hz), 3.98(s, 2H), 7.15-7.21(m, 2H), 7.25(d, 4H, J=4.3 Hz), 7.60(dd, 1H, J=7.1, 1.5 Hz), 7.98(dd, 1H, J=8.1, 1.5 Hz), 8.43(d, 1H, J=7.6 Hz), 11.34(s, 1H), 13.70(s, 1H).

Example 62:

2-({[5-(2-cyclohexylethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO); 0.81-0.94(m, 2H), 1.02-1.30(m, 4H), 1.55-1.73(m, 7H), 2.92(t, 2H, J=7.8 Hz), 3.97(s, 2H), 7.17(t, 1H, J=7.3 Hz), 7.58(dt, 1H, J=7.0, 1.5 Hz), 7.97(dd, 1H, J=8.0, 1.5 Hz), 8.42(d, 1H, J=8.3 Hz), 11.41(br s, 1H), 13.58(br s, 1H).

Example 63:
2-({[5-(cyclopentylmethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 1.14-1.27(m, 2H), 1.43-1.67(m, 4H), 1.69-1.82(m, 2H), 2.20-2.31(m, 1H), 2.93(d, 2H, J=7.3 Hz), 3.98(s, 2H), 7.17(t, 1H, J=7.5 Hz), 7.58(dt, 1H, J=7.0, 1.0 Hz), 7.97(dd, 1H, J=7.8, 1.3 Hz), 8.43(d, 1H, J=8.3 Hz), 11.43(br s, 1H), 13.62(br s, 1H).

Example 64:
2-({[5-(2-cyclopentylethyl)-1,2,4-oxadiazol-3-yl]acetyl}amino)benzoic acid

NMR δ_H (400MHz, d^6-DMSO) 1.01-1.14(m, 2H), 1.36-1.64(m, 4H), 1.64-1.82(m, 5H), 2.92(t, 2H, J=7.3 Hz), 3.98(s, 2H), 7.17(dt, 1H, J=7.1, 1.0 Hz), 7.59(dt, 1H, J=7.1, 1.5 Hz), 7.97(dd, 1H, J=8.1, 1.5 Hz), 8.43(d, 1H, J=8.3 Hz), 11.33(br s, 1H), 13.65(br s, 1H).

Example 65:
2-[({5-[(phenyloxy)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

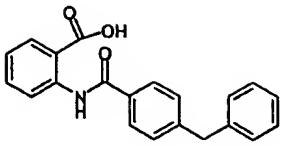
NMR δ_H (400MHz, $CDCl_3$); 3.92(s, 2H), 5.27(s, 2H), 6.91-7.01(m, 3H), 7.05(t, 1H, J=7.3 Hz), 7.26(t, 2H, J=9.1 Hz), 7.46(t, 1H, J=7.3 Hz), 8.01(d, 1H, J=7.8 Hz), 8.59(d, 1H, J=8.3 Hz), 11.57(s, 1H), one exchangeable proton not observed to δ_H 13.

Example 66:
2-[({5-[(phenylthio)methyl]-1,2,4-oxadiazol-3-yl}acetyl)amino]benzoic acid

NMR δ_H (400MHz, $CDCl_3$); 4.03(s, 2H), 4.24(s, 2H), 7.11(t, 1H, J=7.5 Hz), 7.18-7.29(m, 2H), 7.40(d, 1H, J=7.0 Hz), 7.50-7.60(m, 2H), 7.72(dd, 1H, J=5.5, 3.3 Hz), 8.04(d, 1H, J=7.8 Hz), 8.66(d, 1H, J=8.3 Hz), 11.37(br s, 1H), one exchangeable proton not observed to δ_H 13.

D. Example Compound Synthesised Using Method D.

Example 67: 2-({[4-(phenylmethyl)phenyl]carbonyl}amino)benzoic acid



a) 2-[4-(phenylmethyl)phenyl]-4*H*-3,1-benzoxazin-4-one

To 4-(phenylmethyl)benzoic acid (92mg, 0.43mmol) in THF (5ml) was added carbonyl diiimidazole (85mg, 0.45mmol) and the solution stirred for 1h. Anthranilic acid (60mg, 0.44mmol) was added to the solution followed by pyridinium *p*-toluenesulfonate (240mg, 0.96mmol). The mixture was heated at 70°C for 18h, cooled, filtered and concentrated. Chromatography (3:1 cyclohexane/ethyl acetate as eluent) over silica yielded product as a white solid (40mg, 29%). δ_H (400MHz, $CDCl_3$) 4.1 (2H, s), 7.2-7.38 (8H, m), 7.52 (1H, app t, J=8Hz), 7.7 (1H, d, J=8Hz), 7.83 (1H, app t, J=8Hz), 8.25 (2H, d, J=8Hz). m/z 314 [MH^+]

b) 2-({[4-(phenylmethyl)phenyl]carbonyl}amino)benzoic acid

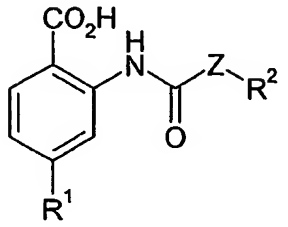
2-[4-(phenylmethyl)phenyl]-4*H*-3,1-benzoxazin-4-one (40mg, 0.13mmol) was suspended in 1:1 dioxan/water (1ml) containing sodium hydroxide (5.1mg, 0.13mmol) and the mixture stirred for 24h then concentrated to yield a white solid which was washed with ether and dried to provide the title compound as the sodium salt (37mg, 86%); δ_H (400MHz, d^6-DMSO) 4.02 (2H, s), 6.97 (1H, app t, J=8Hz), 7.18-7.40 (8H, m), 7.94 (2H, d, J=8Hz), 8.03 (1H, d, J=8Hz), 8.64 (1H, d, J=8Hz), 15.44 (1H, s). m/z 332 [MH^+]

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

Claims

1. An compound selected from: a compound of Formula (I)



(I)

and a salt, solvate or physiologically functional derivative thereof, wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

Z represents $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_nO-$; $-C(R^4R^5)O-$ or -Y-W-X- ;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$; $-(CH_2)_pS-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 and 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

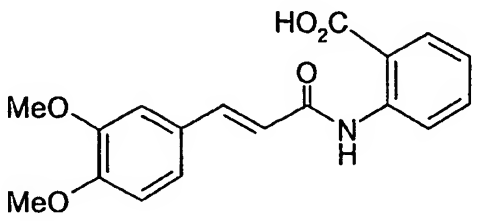
R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl;

provided

(i) that when R^1 is hydrogen, Z is $-(CH_2)_n-$, and n is 2, then R^2 is other than para-chlorophenyl or para-methylphenyl and

(ii) that a compound of Formula (I) is other than 2-(2-(((4-(phenyl)phenyl) amino)acetyl)amino)benzoic acid, 2-(2-(((4-phenyl)phenoxy)acetyl)amino) benzoic acid, 2-[[(4-cyclohexylphenoxy)acetyl]amino]benzoic acid, 2-[[3-[3-(4-

chlorophenyl)-1,2,4-oxadiazol-5-yl]-1-oxopropyl]amino]benzoic acid or compound X



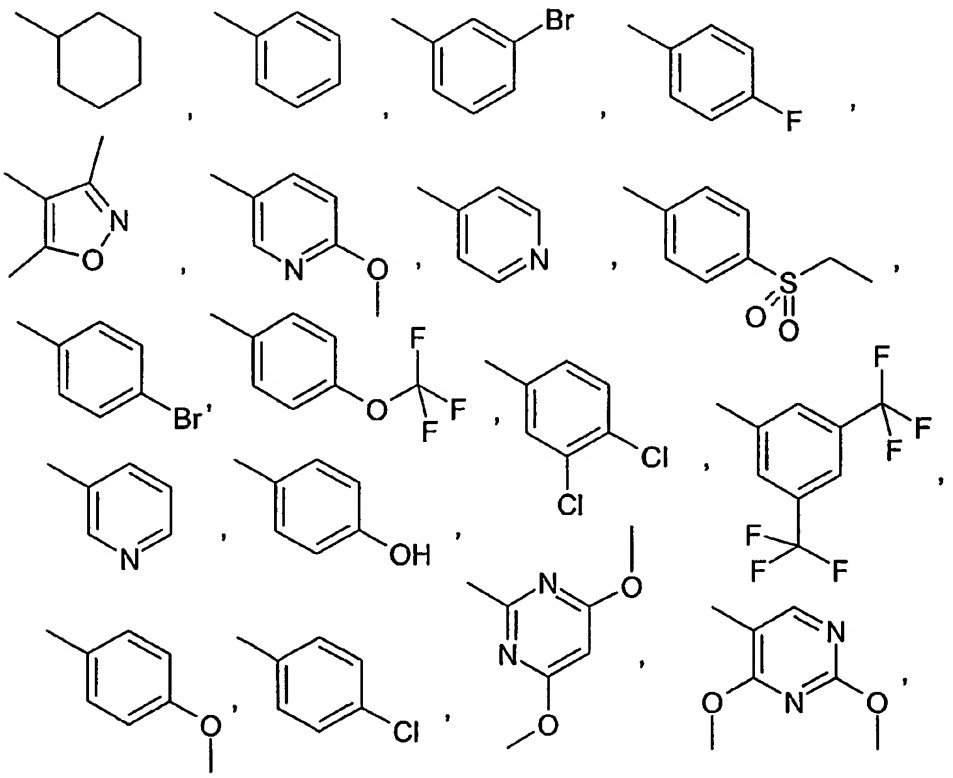
X.

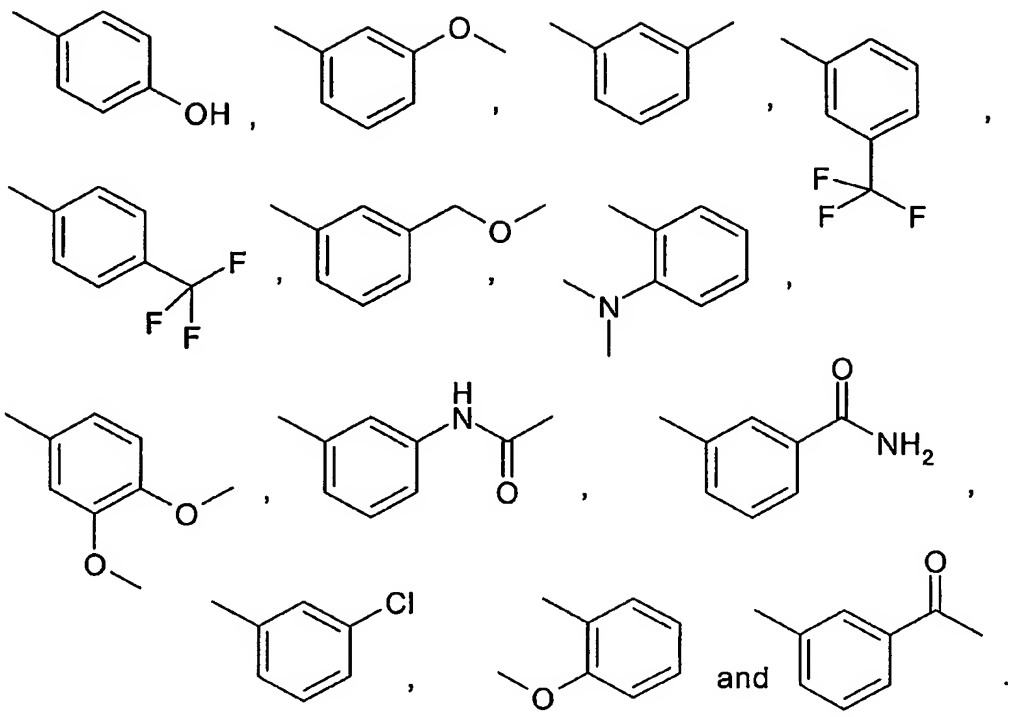
2. A compound according to claim 1 wherein R^1 is hydrogen or methyl.

3. A compound according to claim 2 wherein R^1 is hydrogen.

4. A compound according to any preceding claim wherein R^2 is cyclohexyl, phenyl, pyridinyl, pyrimidinyl, pyridazinyl and isoxazolyl.

5. A compound according to any one of claims 1-3 wherein R^2 is selected from the group consisting of:





6. A compound according to any one of claims 1-3 wherein R^2 is substituted phenyl.

7. A compound according to claim 6 wherein R^2 is phenyl substituted with one or two substituents selected from halogen C_{1-3}alkyl, C_{1-3}haloalkyl C_{1-3}alkoxy and C_{1-3}haloakloxy.

8. A compound according to any preceding claim wherein Y is –O– , $-CH_2-$ or $-CH_2O-$.

9. A compound according to any preceding claim wherein X is absent or is $-SO_2NR^3-$, –NHC(O)– or –NHC(O)NH– .

10. A compound according to any preceding claim wherein Y is $-CH_2-$ and X is $-SO_2NR^3-$.

11. A compound according to any one of claims 1- 7 wherein Y is –O– and X is absent.

12. A compound according to any preceding claim wherein W is a 5 or 6 member aryl or heteroaryl ring.

13. A compound according to claim 12 wherein W is phenyl.

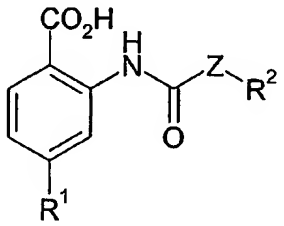
14. A compound according to claim 12 wherein W is a 5 member heteroaryl ring.

15. A compound according to any preceding claim for use in human or veterinary medicine

16. A compound according to any one of claims 1-14 for use in the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions.

17. Use of compound according to any one of claims 1-14 in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions.

18. A compound selected from: a compound of Formula (Ia)



(Ia)

and a salt, solvate or physiologically functional derivative thereof, for use in the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

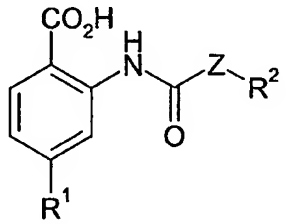
q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

19. A compound according to claim 18 wherein the use is in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesterolaemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.

20. Use of a compound selected from: a compound of Formula (Ia)



(Ia)

and a salt, solvate or physiologically functional derivative thereof in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or of inflammatory diseases or conditions

wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or $-Y-W-X-$;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

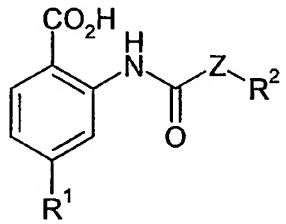
p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

21. A method for the treatment of a human or animal subject having disease characterised by under-activation of the HM74A receptor or in which activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound selected from: a compound of Formula (Ia)



(Ia)

And a salt, solvate or physiologically functional derivative thereof wherein:

R^1 represents hydrogen, halogen or C_1-C_3alkyl;

R^2 represents a 5 or 6-member aryl, heteroaryl, or heterocyclic or alicyclic ring;

Z represents $-(CH_2)_n-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_qO-$; $-C(R^4R^5)O-$ or–Y-W-X– ;

W represents a 5 or 6-member aryl, heteroaryl, heterocyclic or alicyclic ring;

X and Y, which may independently be present or absent, where present independently represent $-(CH_2)_q-$; $-CH=CH-$; $-(CH_2)_pNHC(O)-$; $-(CH_2)_pNHC(O)O-$; $-(CH_2)_pNHC(O)NH-$; $-(CH_2)_pSO_2NR^3-$; $-(CH_2)_pNR^3SO_2-$; $-(CH_2)_pC(O)-$; $-(CH_2)_pNH-$; $-(CH_2)_pO-$ or $-(CH_2)_pO-CH_2-$;

n represents an integer selected from 2, 3 and 4;

p represents an integer selected from 0, 1 or 2;

q represents an integer selected from 1, 2, 3 and 4;

R^3 represents hydrogen or methyl; and

R^4 and R^5 , which may be the same or different, independently represent C_1-C_3alkyl.

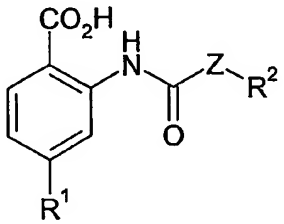
22. A method according to claim 21 wherein the condition is a disorder of lipid metabolism including dislipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

23. A pharmaceutical formulation comprising a compound according to any one of claims 1-14 in admixture with one or more physiologically acceptable diluents, excipients or carriers.

24. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising a compound according to any one of claims 1-14 together with another therapeutically active agent.

25. A pharmaceutical formulation comprising a compound according to any one of claims 1-14, plus a further active ingredient selected from the group consisting of statins, fibrates, bile-acid binding resins and nicotinic acid and one or more physiologically acceptable diluents, excipients or carriers.

26. A method for the preparation of a compound of Formula (I)



(I)

in which R^1 represents hydrogen, Z represents -Y-W-X-, Y represents $-(CH_2)_pO-$, p represents the integer 1, and W, X and R^2 are as defined in claim 1, the method comprising the steps of:

(i) amide bond formation by acetylation of an ester of anthranilic acid;

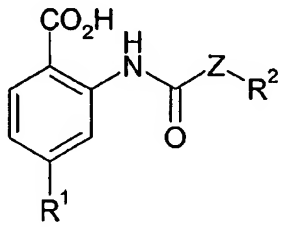
(ii) addition of W or W-X-R^2 by substitution of a leaving group;

(iii) deprotection of the anthranilic acid group;

and where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

27. A method according to claim 26 where in step (ii) comprises addition of W and a further step (ii)(a), addition of R^2, is included in the form of a further substitution reaction.

28. A method for the preparation of a compound of Formula (I)



(I)

the method comprising the steps of:

(i) formation of an amide between the amine group of 2-amino-bezoic acid and an activated acyl transfer reagent derived from a carboxylic acid

(ii) where desired or necessary converting a resultant free acid or base compound of Formula (I) into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

INTERNATIONAL SEARCH REPORT

GB2004/003528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C235/38 C07D307/52 C07D213/65 C07D231/12 C07D271/06
C07D333/24 A61K31/4412 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/07669 A (AMERICAN HOME PROD) 18 February 1999 (1999-02-18) claim 1; examples 15,19,25	1,18
X	FR 2 763 334 A (LIPHA) 20 November 1998 (1998-11-20) claim 1; examples 1-17	1,18
X	PATENT ABSTRACTS OF JAPAN vol. 0092, no. 41 (C-306), 27 September 1985 (1985-09-27) -& JP 60 097946 A (ONO YAKUHIN KOGYO KK), 31 May 1985 (1985-05-31) abstract; claim 2; compounds A-D	1,18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 2004	09/12/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Seelmann, I

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INTERNATIONAL SEARCH REPORT

GB2004/003528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WISE A ET AL: "MOLECULAR IDENTIFICATION OF HIGH AND LOW AFFINITY RECEPTORS FOR NICOTINIC ACID" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 278, no. 11, 14 March 2003 (2003-03-14), pages 9869-9874, XP009011556 ISSN: 0021-9258 table 2	1-28

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